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(54) Title: HIV PROTEASE INHIBITORS

(57) Abstract

Oligopeptide analogs are described. These compounds are useful in the inhibition of HIV protease, the prevention or treatment of infection by HIV and the treatment of AIDS, either as compounds, pharmaceutically acceptable salts, pharmaceutical composition ingredients, whether or not in combination with other antivirals, immunomodulators, antibiotics or vaccines. Methods of treating AIDS and methods of preventing or treating infection by HIV are also described.

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TITLE OF THE INVENTION
HIV PROTEASE INHIBITORS

This application is related to Merck Case 18466, Serial No. 07/746,460, filed August 16, 1991; Merck Case 18583, Serial No. 07/781,470, filed October 13, 1991; Merck Case 18583IA, Serial No. 07/929,991, filed August 21, 1992; Merck Case 18882, Serial No. 08/017,090, filed February 12, 1993.

The present invention is concerned with compounds which inhibit the protease encoded by human immunodeficiency virus (HIV). The compounds, or pharmaceutically acceptable salts thereof, are of value in the prevention of infection by HIV, the treatment of infection by HIV and the treatment of the resulting acquired immune deficiency syndrome (AIDS).

The present invention also relates to pharmaceutical compositions containing the compounds and to a method of use of the present compounds and other agents for the treatment of AIDS & viral infection by HIV.

BACKGROUND OF THE INVENTION

A retrovirus designated human immunodeficiency virus (HIV) is the etiological agent of the complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome; AIDS) and degeneration of the central and peripheral nervous system. This virus was previously known as LAV, HTLV-III, or ARV. A common feature of retrovirus replication is the extensive post-translational processing of precursor polyproteins by a virally encoded protease to generate mature viral proteins required for virus assembly and function. Inhibition of this processing prevents the production of normally infectious virus. For example, Kohl, N.E., et. al., Proc. Natl. Acad. Sci. USA, 85, 4686 (1988), demonstrated that genetic inactivation of the HIV encoded protease resulted in the production of immature, non-infectious virus particles. These results suggest that inhibition of the HIV protease represents a viable method

for the treatment of AIDS and the prevention or treatment of infection by HIV.

Nucleotide sequencing of HIV shows the presence of a pol gene in one open reading frame [Ratner, L. et al., Nature, 313, 277(1985)]. Amino acid sequence homology provides evidence that the pol sequence encodes reverse transcriptase, an endonuclease and an HIV protease [Toh, H. et al., EMBO J. 4, 1267 (1985); Power, M.D. et al., Science, 231, 1567 (1986); Pearl, L.H. et al., Nature 329, 351 (1987)]. Applicants demonstrate that the compounds of this invention are inhibitors of HIV protease.

Related art includes Hoffman-LaRoche EPO applications. EPO 389898, EPO 346847, and EPO 432695 each disclose HIV protease inhibitors but the compounds are very different because they have an amino acid (or analog thereof) attached to the amino-terminal end of the transition state analog. EPO 432694 discloses synthetic intermediates which are different from the compounds of the present invention.

The particular advantages of the compounds of the present invention are the combination of high antiviral activity and lowered molecular weight.

BRIEF DESCRIPTION OF THE INVENTION

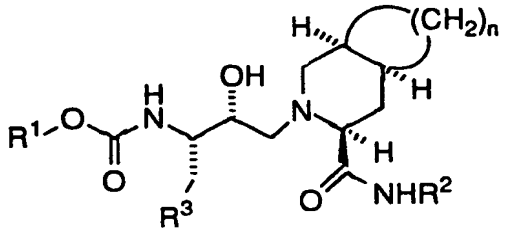
Compounds of formula I, as herein defined, are disclosed. These compounds are useful in the inhibition of HIV protease, the prevention of infection by HIV, the treatment of infection by HIV and in the treatment of AIDS, either as compounds, pharmaceutically acceptable salts, hydrates or esters, pharmaceutical composition ingredients, whether or not in combination with other antivirals, immunomodulators, antibiotics or vaccines. Methods of treating AIDS, methods of preventing infection by HIV, and methods of treating infection by HIV are also disclosed.

ABBREVIATIONS

	Activating Agent
HBT (HOBT or HOBt)	1-hydroxybenzotriazole hydrate
	Condensing Agent
EDC	1-ethyl-3-(3-dimethylamino-propyl)carbodiimide

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

This invention is concerned with the compounds of Formula I, combinations thereof, or pharmaceutically acceptable salts thereof, in the inhibition of HIV protease, the prevention of infection by HIV, the treatment of infection by HIV and in the treatment of the resulting acquired immune deficiency syndrome (AIDS). Compounds of formula I are defined as follows:



(I)

wherein:

n is 3 or 4;

R^1 is a 7- to 10-membered bicyclic heterocycle, either ring of which is saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen or sulfur heteroatoms may optionally be oxidized,

said heterocycle being unsubstituted or substituted with one or more of C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-3} alkoxy, halo-C_{1-3} alkyl, aryl-C_{1-3} alkyl, C_{3-5} cycloalkyl, di-C_{1-3}-alkyl-amino-C_{1-4} alkyl, halo or aryl;

R^2 is
a) C_{1-5} alkyl, unsubstituted or substituted with one or more of -OH or C_{1-3} alkoxy; or
b) 5- to 7-membered carbocyclic ring which is either saturated, partially saturated or unsaturated, the carbocyclic ring being unsubstituted or substituted with one or more of C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-3} alkoxy, or hydroxy;

R^3 is
a) Phenyl unsubstituted or substituted with one or more of -OH or C_{1-3} alkoxy; or
b) C_{5-7} cycloalkyl unsubstituted or substituted with one or more of -OH or C_{1-3} alkoxy,

or pharmaceutically acceptable salt or hydrate thereof.

The compounds of the present invention may have asymmetric centers and occur as racemates, racemic mixtures and as individual diastereomers or enantiomers, with all isomeric forms being included in the present invention.

When any variable (e.g., C_{1-5} alkyl, R^1 or R^2, etc.) occurs more than one time in any constituent or in formula I, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein except where noted, "alkyl" is intended to include both branched- and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms (Me is methyl, Et is ethyl, Pr is propyl, Bu is butyl); "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge. "Alkenyl" is intended to include hydrocarbon claims of

either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl, propenyl, butenyl, pentenyl, and the like. "Halo", as used herein, means fluoro, chloro, bromo or iodo.

As used herein, with exceptions as noted, "aryl" is intended to mean phenyl (Ph) or naphthyl. "Carbocyclic" is intended to mean any stable 5- to 7-membered carbon ring or 7- to 10-membered bicyclic carbon ring, any of which may be saturated or partially unsaturated.

The term heterocycle or heterocyclic, as used herein except where noted, represents a stable 5- to 7-membered mono- or bicyclic or stable 7- to 10-membered bicyclic heterocyclic ring system any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements include piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, thiadiazoyl, benzopyranyl, enzothiopyranyl, tetrahydrofuryl, tetrahydropyranyl, and tetrahydrothienyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone and isobenzothiopyranyl.

The pharmaceutically-acceptable salts of the compounds of Formula I (in the form of water- or oil-soluble or dispersible products) include the conventional non-toxic salts or the quaternary ammonium salts of these compounds, which are formed, e.g., from inorganic or organic acids. Examples of such acid addition salts include acetate,

adipate, alginate, aspartate, benzoate, bisulfate, citrate, digluconate, dodecylsulfate, fumarate, glycerophosphate, hemisulfate, hydrochloride, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, succinate and tartrate.

In a preferred embodiment of this invention,

R^1 is a 7- to 10-membered bicyclic heterocycle, either ring of which is saturated or unsaturated, and which consists of carbon atoms and from one to three oxygen heteroatoms, said heterocycle being unsubstituted or substituted with one or more of C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-3} alkoxy, halo-C_{1-3} alkyl, aryl-C_{1-3} alkyl, C_{3-5} cycloalkyl, di-C_{1-3} alkyl-amino-C_{1-4} alkyl, halo or aryl;

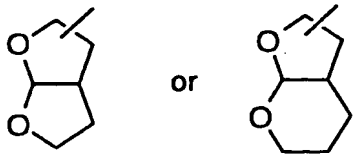
R^2 is C_{1-5} alkyl, unsubstituted or substituted with one or more of -OH;

R^3 is phenyl unsubstituted or substituted with -OH or C_{1-3} alkoxy,

or pharmaceutically acceptable salt or hydrate thereof.

A third embodiment is further limited to compounds wherein:

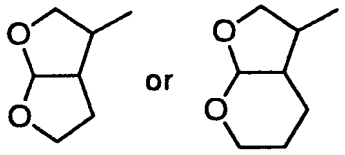
R^1 is a bicyclic heterocycle of the structures:



said heterocycle unsubstituted or substituted once with C_{1-4} alkyl, methoxy, dimethylaminometyl, halo or aryl;

R^2 is t-butyl or 2-methylpropyl;
R^3 is phenyl.

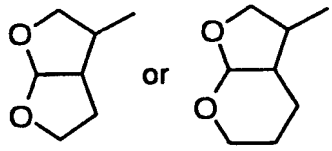
A fourth embodiment is further limited to compound wherein:
R^1 is:



either of which structure is unsubstituted or substituted once with C_{1-4} alkyl, methoxy, dimethylaminomethyl, halo or aryl;

R^2 is t-butyl or 2-methylpropyl;
R^3 is phenyl.

In a fifth preferred embodiment,
R^1 is

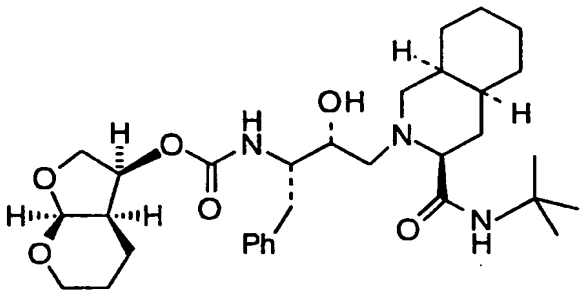


and,
R^2 is t-butyl;
R^3 is phenyl.

Most preferred compounds of this invention include the following, in approximate order of decreasing potency:

The compound [L-739,684], the most preferred:

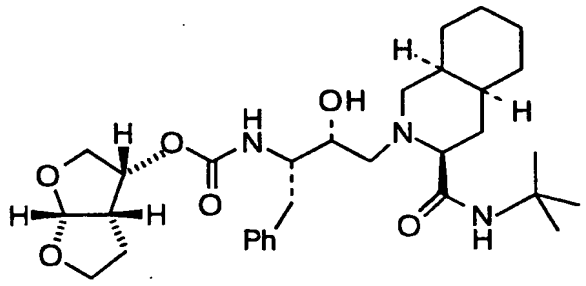
B:



named:
(3S,4aS,8aS,2'R,3'S,3"S, 3"aR,7"aS) N-tert-Butyl 2(2'-hydroxy-4'-phenyl-3'(3"-hexahydro-4"H-furo[2,3-b]pyranyloxycarbonylamino)-butyl)-decahydroisoquinoline-3-carboxamide
or pharmaceutically acceptable salt thereof.

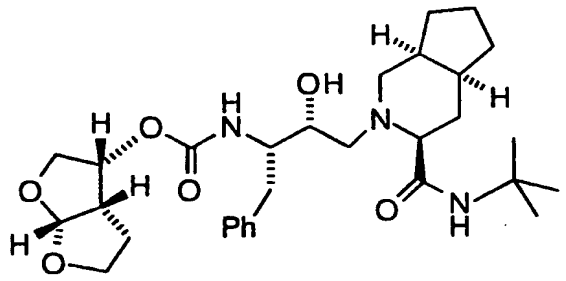
The compound [L-739,594]

C:



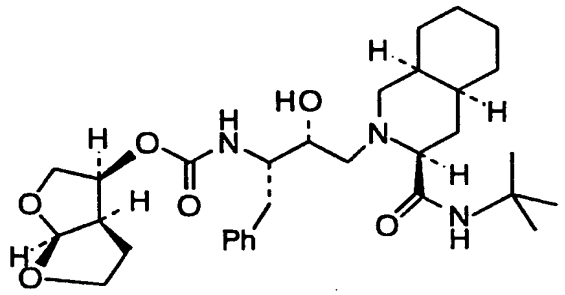
named:
(3S,4aS,8aS,2'R,3'S,3"R,3"aS,6"aR) N-tert-butyl 2(2'-hydroxy-4'-phenyl-3'(3"-hexahydrofuro[2,3-b]furanyloxycarbonylamino)butyl)-decahydroisoquinoline-3-carboxamide,
or pharmaceutically acceptable salt thereof.

The compound [L-741,129]



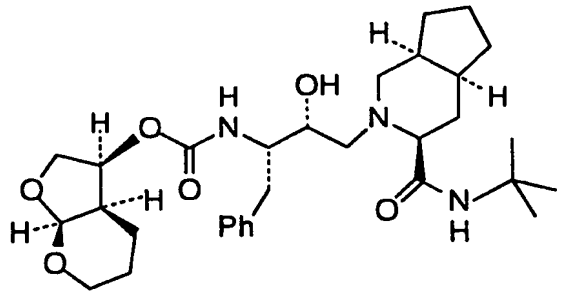
named:
(3S,4aS,7aS,2'R,3'S,3"R,3"aS,6"aR) N-tert-Butyl octahydro-2(2'-hydroxy-4'-phenyl-3'(3"-hexahydrofuro[2,3-b]furanyloxycarbonyl-amino)butyl)-1H-pyrindene-3-carboxamide,
or pharmaceutically acceptable salt thereof.

D. The compound, [L-739,663]



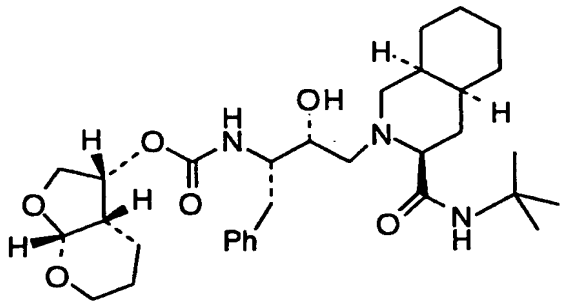
named:
(3S,4aS,8aS,2'R,3'S,3"S,3"aR,6"aS) N-tert-Butyl 2(2'-hydroxy-4'-phenyl-3'(3"-hexahydrofuro[2,3-b]furanyloxycarbonylamino)butyl)-decahydroisoquinoline-3-carboxamide,
or pharmaceutically acceptable salt thereof.

E. The compound, [L-743,639]



named:
(3S,4aS,7aS,2'R,3'S,3"S,3"aR,7"aS) N-tert-butyl octahydro-2(2'-hydroxy-4'-phenyl-3'(3"-hexahydro-4"H-furo[2,3-b]pyranloxycarbonyl-amino)butyl)-1H-pyrindene-3-carboxamide,
or pharmaceutically acceptable salt thereof.

F. The compound, [L-739,761]



named:
(3S,4aS,8aS,2'R,3'S,3"R,3"aS,7"aR) N-tert-Butyl 2(2'-hydroxy-4'-phenyl-3'(3"-hexahydro-4"H-furo{2,3-b]pyranyloxycarbonyl-amino)butyl)-decahydroisoquinoline-3-carboxamide,
or pharmaceutically acceptable salt thereof.

Other preferred compounds include, but are not limited to, the following:

(3S,4aS,8aS,2'R,3'S,3"S,3"aR,5"R,7"aS) N-tert-butyl 2(2'-hydroxy-4'-phenyl-3'(6"-methyl-3"-hexahydro-4H-furo[2,3-b]pyranyloxy-carbonylamino)butyl)-decahydroisoquinoline-3-carboxamide,

(3S,4aS,8aS,2'R,3'S,3"R,3"aS,5"S,6"aR) N-tert-butyl 2(2'-hydroxy-4'-phenyl-3'(5"-methyl-3"-hexahydrofuro[2,3-b]furanyloxy-carbonylamino)butyl)-decahydroisoquinoline-3-carboxamide (L-739,783),

(3S,4aS,8aS,2'R,3'S,2"S,3"S,3"aR,7"aS) and (3S,4aS,8aS,2'R,3'S,2"R,3"R,3"aS,7"aR) N-tert-Butyl 2(2'-hydroxy-4'-phenyl-3'(2"-methyl-3"-hexahydro-4"H-furo[2,3-b]pyranyloxy-carbonylamino)butyl)-decahydroisoquinoline-3-carboxamide (L-743,787),

(3S,4aS,8aS,2'R,3'S,2"R,3"S,3"aR,7"aS) and (3S,4aS,8aS,2'R,3'S,2"S,3"R,3"aS,7"aR) N-tert-Butyl 2(2'-hydroxy-4'-phenyl-3'(2"-methyl-3"-hexahydro-4"H-furo[2,3-b]pyranyloxy-carbonylamino)butyl)-decahydroisoquinoline-3-carboxamide (L-743,788),

(3S,4aS,8aS,2'R,3'S,2"S,3"S,3"aR,6"aS) and (3S,4aS,8aS,2'R,3'S,2"R,3"R,3"aS,6"aR) N-tert-Butyl 2(2'-hydroxy-4'-phenyl-3'(2"-methyl-3"-hexahydrofuro[2,3-b]furanyloxycarbonyl-amino)butyl)-decahydroisoquinoline-3-carboxamide,

(3S,4aS,8aS,2'R,3'S,3"R,3"aS,5"R,6"aR) N-tert-butyl 2(2'-hydroxy-4'-phenyl-3'(5"-methyl-3"-hexahydrofuro[2,3-b]furanyloxy-carbonylamino)butyl)-decahydroisoquinoline-3-carboxamide L-743,768),

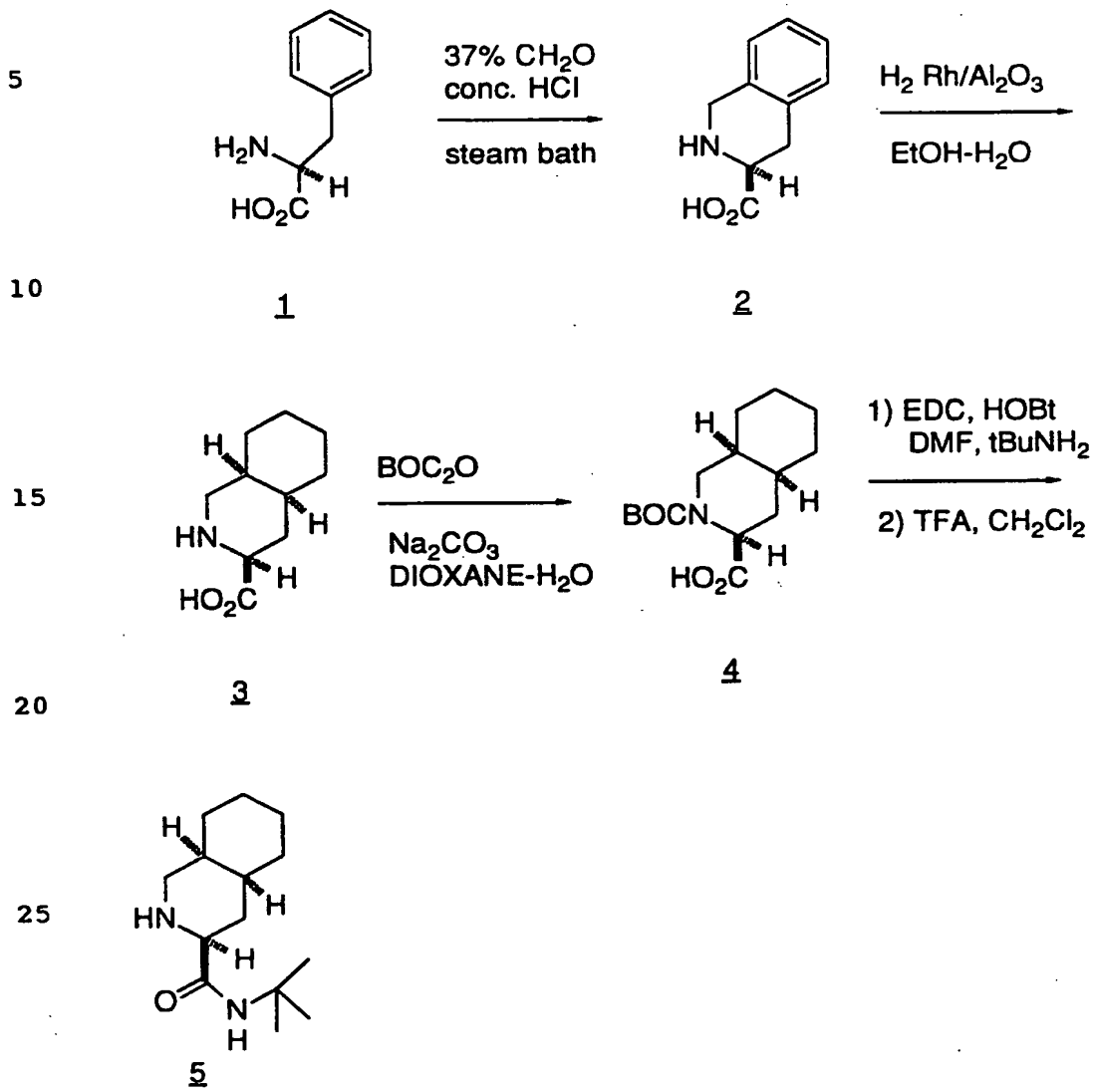
(3S,4aS,8aS,2'R,3'S,3"aS,4"S,6"aR) N-tert-Butyl 2(2'-hydroxy-4'-phenyl-3'-(4"-hexahydro-2H-cyclopenta[b]furanyloxycarbonylamino)-butyl)-decahydroisoquinoline-3-carboxamide (L-743,707), or

(3S,4aS,8aS,2'R,3'S,3"aR,4"R,6"aS) N-tert-Butyl 2(2'-hydroxy-4'-phenyl-3'-(4"-hexahydro-2H-cyclopenta[b]furanyloxycarbonylamino)-butyl)-decahydroisoquinoline-3-carboxamide (L-743,770),

or pharmaceutically acceptable salts thereof.

The compounds of the present invention are prepared in accordance with Schemes I-IV.

SCHEME I

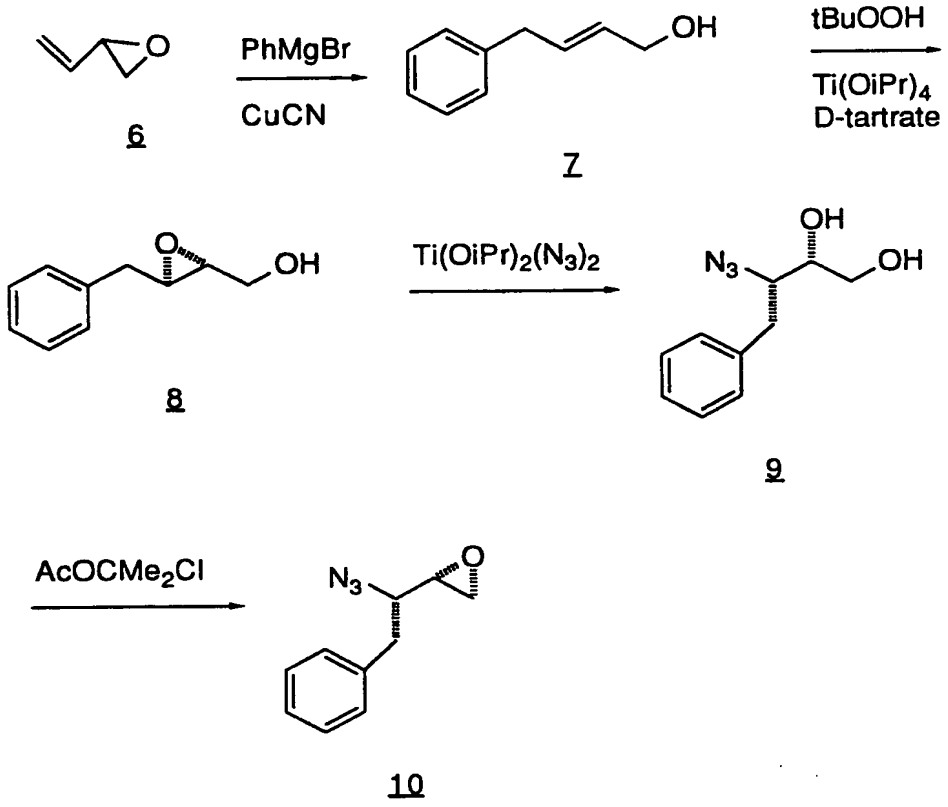


1 2 3 4 5

The decahydro-isoquinoline intermediate 5 is synthesized by a first reaction of L-phenylalanine with formaldehyde and concentrated HCl to produce 2, as also described in Skiles, J.W. et al., J.

Med. Chem. 29, 784 (1986) Hein, G.E., et al., J. Am. Chem. Soc. 48, 4487 (1962) and Hayasnik, K. et al., Chem. Pharm. Bull. 31, 312 (1983). Subsequent hydrogenation with catalysts such as Pt or Rh yields 3, which is then derivatized with an NH-protecting group such as Boc to give 4. Coupling with $tBuNH_2$ followed by deprotection affords 5. Example 1 illustrates but does not limit Scheme I.

SCHEME II

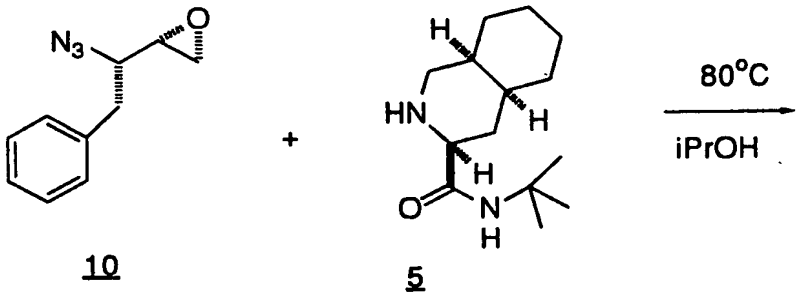


6 7 8 9 10

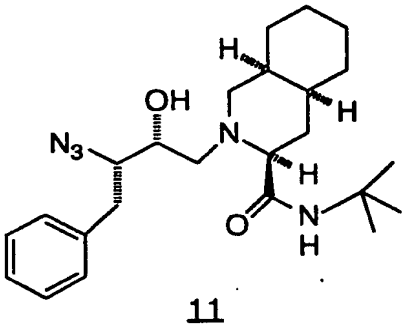
Catalytic asymmetric or Sharpless epoxidation to produce 8 is performed by the methods of Gao, Y. et al., J. Am. Chem. Soc. 109, 5765 (1987). Regio-selective azide opening of the 2,3-epoxy alcohol 8

to give 9 is facilitated by titanium according to Caron, M. et al., J. Org. Chem. 53, 5185 (1988). Example 2 illustrates but does not limit Scheme II.

SCHEME III



10 + 5



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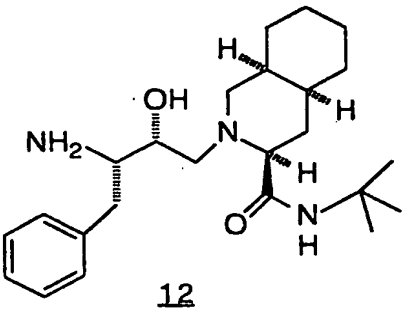

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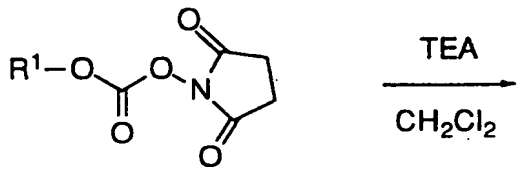

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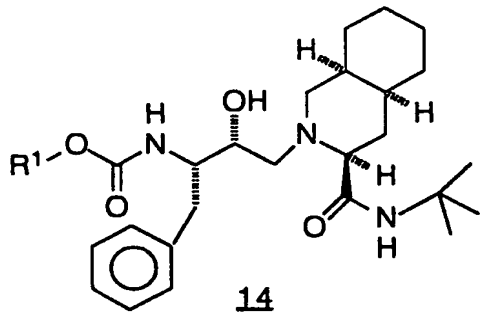

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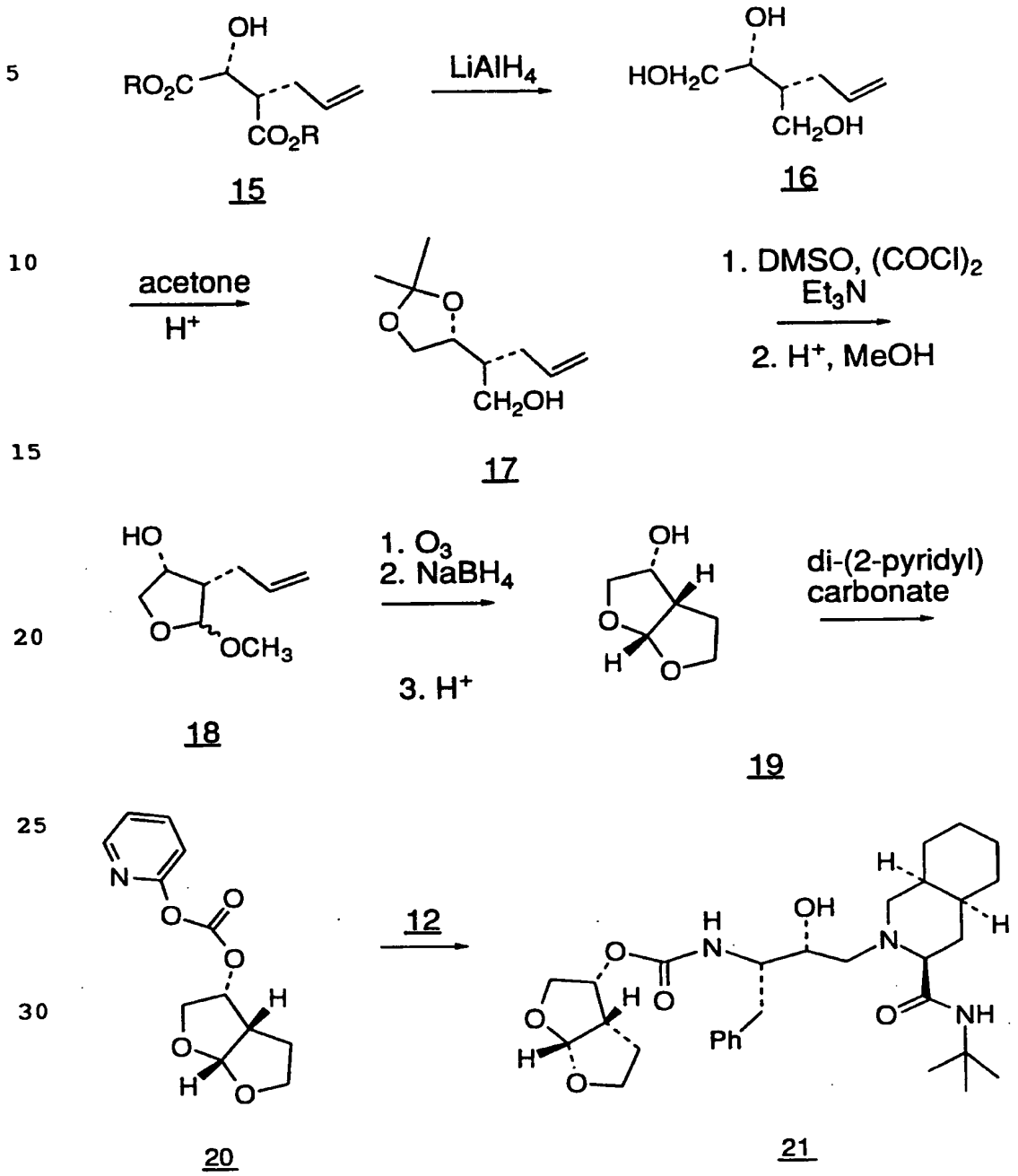
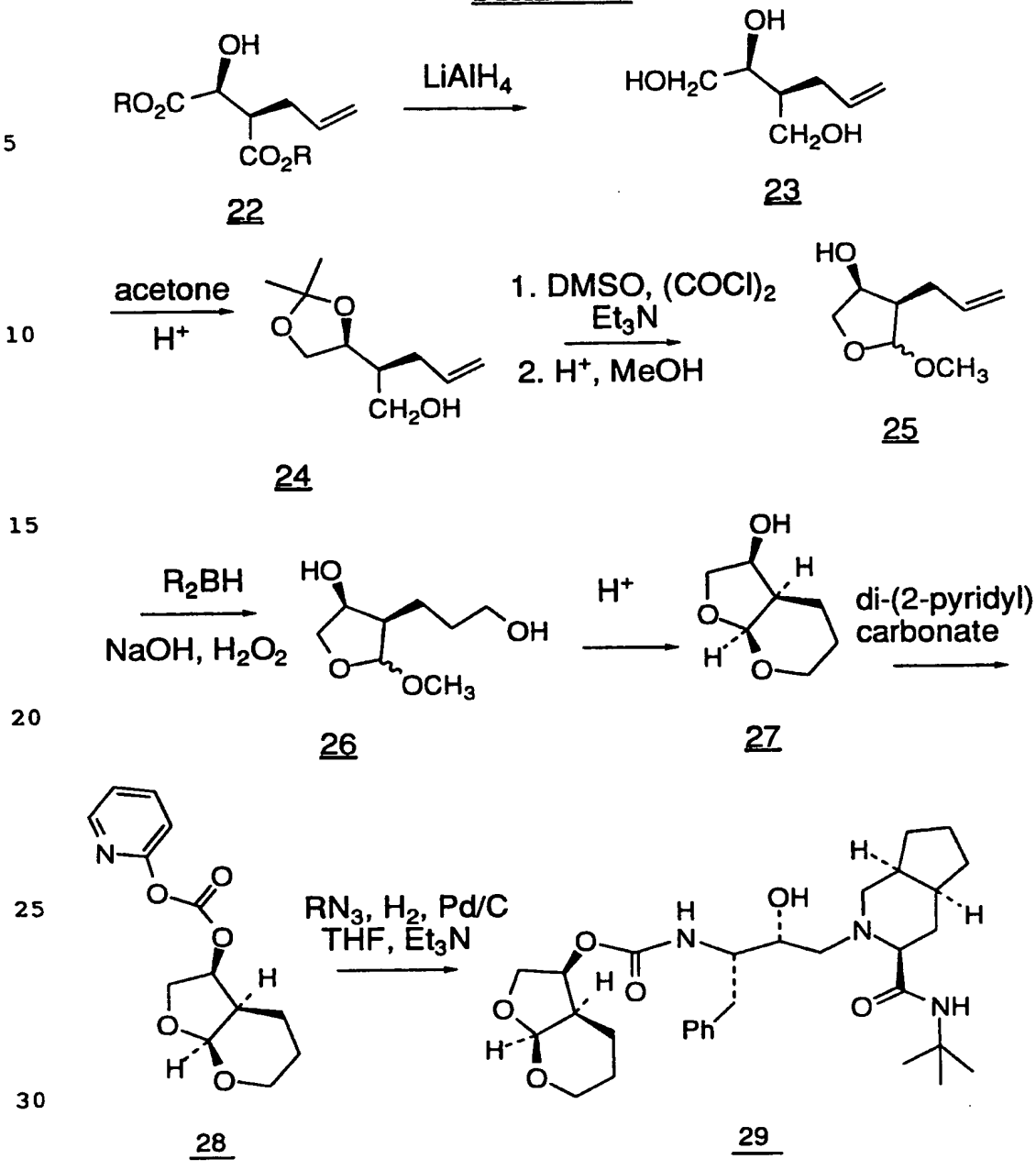
Condensation of the azide epoxide 10 with the decahydroisoquinoline intermediate 5 is performed by, for example, heating a mixture in refluxing isopropanol, to give the azido-alcohol 11 in good yield. Reduction over palladium on carbon yields the amine 12, which is then reacted with the appropriate N-substituted succinimide 13 in the presence of e.g. TEA to give compounds of Formula I or 14. Examples 3-6 illustrate but do not limit Scheme III.

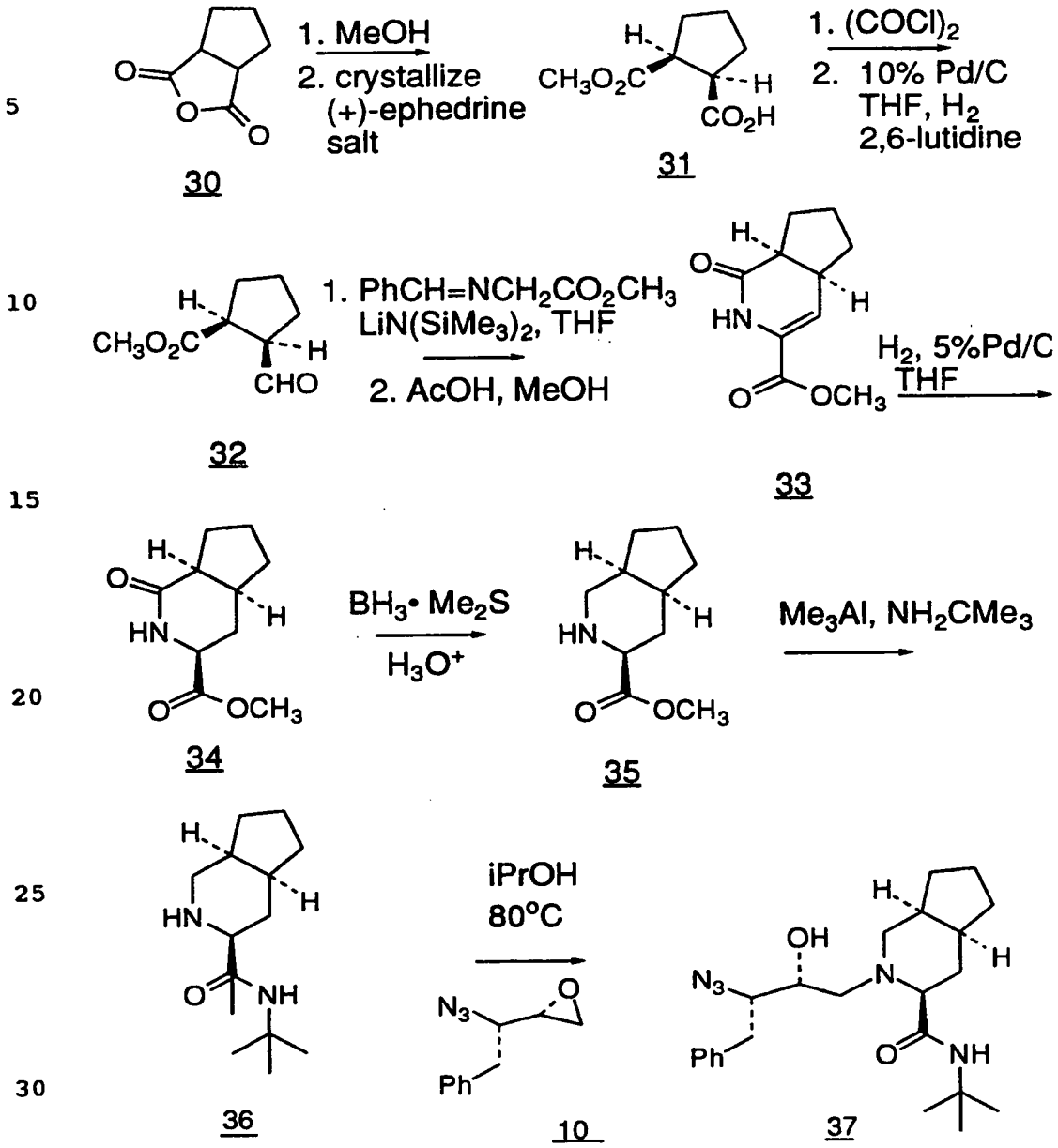
SCHEME IV


OH
RO2C
CO2R
LiAlH4
HOH2C
CH2OH
15
16
acetone
H+
CH2OH
1. DMSO, (COCl)2
Et3N
2. H+, MeOH
17
HO
OCH3
1. O3
2. NaBH4
3. H+
OH
H
di-(2-pyridyl)
carbonate
18
19
N
O
H
12
H
N
OH
N
NH
Ph
20
21

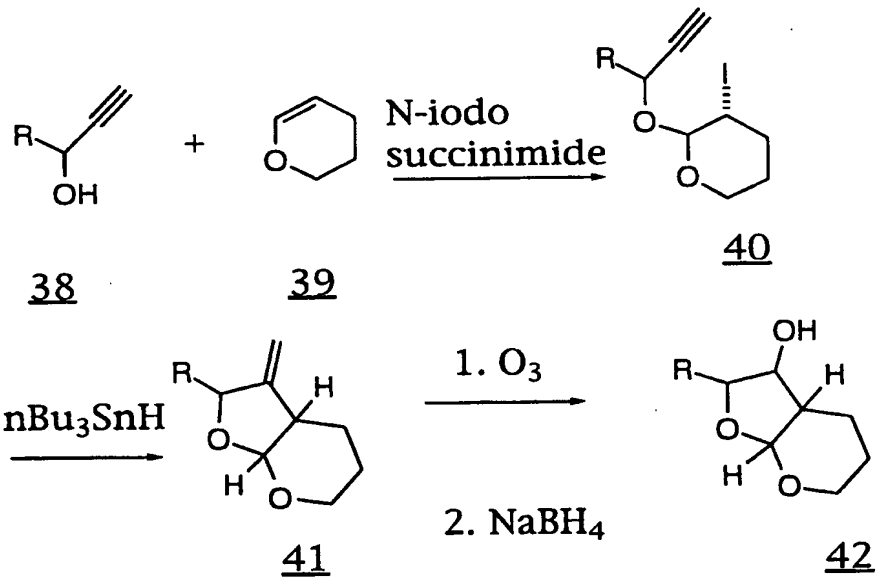
SCHEME V


OH
RO2C
CO2R
LiAlH4
HOH2C
CH2OH
22
23
acetone
H+
CH2OH
1. DMSO, (COCl)2
Et3N
2. H+, MeOH
HO
OCH3
24
25
R2BH
NaOH, H2O2
HO
OH
OCH3
H+
OH
H
di-(2-pyridyl)
carbonate
26
27
RN3, H2, Pd/C
THF, Et3N
N
O
H
Ph
NH
28
29

SCHEME VI


1. MeOH
2. crystallize (+)-ephedrine salt
1. (COCl)2
2. 10% Pd/C THF, H2 2,6-lutidine
1. PhCH=NCH2CO2CH3 LiN(SiMe3)2, THF
2. AcOH, MeOH
H2, 5%Pd/C THF
BH3• Me2S
H3O+
Me3Al, NH2CMe3
iPrOH 80°C
30
31
32
33
34
35
36
10
37

SCHEME VII



38 39 40 41 42

R=H, Me, Et

The compounds of the present invention are useful in the inhibition of HIV protease, the prevention or treatment of infection by the human immunodeficiency virus (HIV) and the treatment of consequent pathological conditions such as AIDS. Treating AIDS or preventing or treating infection by HIV is defined as including, but not limited to, treating a wide range of states of HIV infection: AIDS, ARC (AIDS related complex), both symptomatic and asymtomatic, and actual or potential exposure to HIV. For example, the compounds of this invention are useful in treating infection by HIV after suspected past exposure to HIV by e.g., blood transfusion, accidental needle stick, or exposure to patient blood during surgery.

The compounds of this invention are also useful in the preparation and execution of screening assays for antiviral compounds. For example, the compounds of this invention are useful for isolating enzyme mutants, which are excellent screening tools for more powerful antiviral compounds. Furthermore, the compounds of this invention are

useful in establishing or determining the binding site of other antivirals to HIV protease, e.g., by competitive inhibition. Thus the compounds of this invention are commercial products to be sold for these purposes.

For these purposes, the compounds of the present invention may be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in dosage unit formulations containing conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles.

Thus, in accordance with the present invention there is further provided a method of treating and a pharmaceutical composition for treating HIV infection and AIDS. The treatment involves administering to a patient in need of such treatment a pharmaceutical composition comprising a pharmaceutical carrier and a therapeutically-effective amount of a compound of the present invention, or a pharmaceutically-acceptable salt thereof.

These pharmaceutical compositions may be in the form of orally-administrable suspensions or tablets; nasal sprays; sterile injectable preparations, for example, as sterile injectable aqueous or oleagenous suspensions or suppositories.

When administered orally as a suspension, these compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may contain microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweetners/flavoring agents known in the art. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants known in the art.

When administered by nasal aerosol or inhalation, these compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives,

absorption promoters to enhance bioavailability, flourocarbons, and/or other solubilizing or dispersing agents known in the art.

The injectable solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally-acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

When rectally administered in the form of suppositories, these compositions may be prepared by mixing the drug with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquidify and/or dissolve in the rectal cavity to release the drug.

Dosage levels of the order of 0.02 to 5.0 or 10.0 grams-per-day are useful in the treatment or prevention of the above-indicated conditions, with oral doses two-to-five times higher. For example, infection by HIV is effectively treated by the administration of from 10 to 50 milligrams of the compound per kilogram of body weight from one to three times per day. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age of the patient, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

The present invention is also directed to combinations of the HIV protease-inhibitory compounds with one or more agents useful in the treatment of AIDS. See Table C.

TABLE C

ANTIVIRALS

Drug Name	Manufacturer	Indication
AL-721	Ethigen (Los Angeles, CA)	ARC, PGL HIV positive, AIDS
Recombinant Human Interferon Beta	Triton Biosciences (Almeda, CA)	AIDS, Kaposi's sarcoma, ARC
Cytovene	Syntex	sight threatening CMV
Ganciclovir	(Palo Alto, CA)	peripheral CMV retinitis
d4T Didehydroeoxy-thymidine	Bristol-Myers (New York, NY)	AIDS, ARC
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection (see also immunomodulators)
Trisodium Phosphonoformate	Astra Pharm Products, Inc. (Westborough, MA)	CMV retinitis, HIV infection, other CMV infections
Dideoxycytidine; ddC	Hoffman-LaRoche (Nutley, NJ)	AIDS, ARC

Drug Name	Manufacturer	Indication
Novapren	Novaferon Labs, Inc. (Akron, OH) Diapren, Inc. (Roseville, MN, marketer)	HIV inhibitor
Peptide T Octapeptide Sequence	Peninsula Labs (Belmont, CA)	AIDS
Zidovudine; AZT	Burroughs Wellcome (Rsch. Triangle Park, NC)	AIDS, adv, ARC, pediatric AIDS, Kaposi's sarcoma, asymptomatic HIV infection, less severe HIV disease, neurological involvement, in combination with other therapies.
Ansamycin LM427	Adria Laboratories (Dublin, OH) Erbamont (Stamford, CT)	ARC
Dextran Sulfate	Ueno Fine Chem. Ind. Ltd. (Osaka, Japan)	AIDS, ARC, HIV positive asymptomatic
Virazole Ribavirin	Viratek/ICN (Costa Mesa, CA)	asymptomatic HIV positive, LAS, ARC

Drug Name	Manufacturer	Indication
Alpha Interferon	Burroughs Wellcome (Rsch. Triangle Parks, NC)	Kaposi's sarcoma, HIV in combination w/Retrovir
Acyclovir	Burroughs Wellcome	AIDS, ARC, asymptomatic HIV positive, in combination with AZT.
Antibody which neutralizes pH labile alpha aberrant Interferon in an immunoadsorption column	Advanced Biotherapy Concepts (Rockville, MD)	AIDS, ARC
L-697,661	Merck (Rahway, NJ)	AIDS, ARC, asymptomatic HIV positive, also in combination with AZT.
L-696,229	Merck (Rahway, NJ)	AIDS, ARC, asymptomatic HIV positive, also in combination with AZT.

IMMUNO-MODULATORS

Drug Name	Manufacturer	Indication
AS-101	Wyeth-Ayerst Labs. (Philadelphia, PA)	AIDS
Bropirimine	Upjohn (Kalamazoo, MI)	advanced AIDS
Acemannan	Carrington Labs, Inc. (Irving, TX)	AIDS, ARC (See also antivirals)
CL246,738	American Cyanamid (Pearl River, NY) Lederle Labs (Wayne, NJ)	AIDS, Kaposi's sarcoma
EL10	Elan Corp, PLC (Gainsville, GA)	HIV infection (See also antivirals)
Gamma Interferon	Genentech (S. San Francisco, CA)	ARC, in combination w/TNF (tumor necrosis factor)
Granulocyte Macrophage Colony Stimulating Factor	Hoeschst-Roussel (Somerville, NJ) Immunex (Seattle, WA)	AIDS

Drug Name	Manufacturer	Indication
Granulocyte Macrophage Colony Stimulating Factor	Schering-Plough (Madison, NJ)	AIDS AIDS, in combination w/AZT
HIV Core Particle Immunostimulant	Rorer (Ft. Washington, PA)	seropositive HIV
IL-2 Interleukin-2	Cetus (Emeryville, CA)	AIDS, in combination w/AZT
IL-2 Interleukin-2	Hoffman-La Roche (Nutley, NJ) Immunex	AIDS, ARC, HIV, in combination w/AZT
Immune Globulin Intravenous (human)	Cutter Biological (Berkeley, CA)	pediatric AIDS, in combination w/AZT
IMREG-1	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
IMREG-2	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ACR, PGL
Imuthiol Diethyl Dithio Carbamate	Merieux Institute (Miami, FL)	AIDS, ARC
Alpha-2 Interferon	Schering Plough (Madison, NJ)	Kaposi's sarcoma

Drug Name	Manufacturer	Indication
Methionine-Enkephalin	TNI Pharmaceutical (Chicago, IL)	AIDS, ARC
MTP-PE Muramyl-Tripeptide	Ciba-Geigy Corp. (Summit, NJ)	Kaposi's sarcoma
Granulocyte Colony Stimulating Factor	Amgen (Thousand Oaks, CA)	AIDS, in combination w/AZT
rCD4 Recombinant Soluble Human CD4	Genentech (S. San Francisco, CA)	AIDS, ARC
rCD4-IgG hybrids		AIDS, ARC
Recombinant Soluble Human CD4	Biogen (Cambridge, MA)	AIDS, ARC
Interferon Alfa 2a	Hoffman-La Roche (Nutley, NJ)	Kaposi's sarcoma AIDS, ARC, in combination w/AZT
SK&F106528 Soluble T4	Smith, Kline & French Laboratories (Philadelphia, PA)	HIV infection
Thymopentin	Immunobiology Research Institute (Annandale, NJ)	HIV infection

Drug Name	Manufacturer	Indication
Tumor Necrosis Factor; TNF	Genentech (S. San Francisco, CA)	ARC, in combination w/gamma Interferon

ANTI-INFECTIVES

Drug Name	Manufacturer	Indication
Clindamycin with Primaquine	Upjohn (Kalamazoo, MI)	PCP
Fluconazole	Pfizer (New York, NY)	cryptococcal meningitis, candidiasis
Pastille Nystatin Pastille	Squibb Corp. (Princeton, NJ)	prevention of oral candidiasis
Ornidyl Eflornithine	Merrell Dow (Cincinnati, OH)	PCP
Pentamidine Isethionate (IM & IV)	LyphoMed (Rosemont, IL)	PCP treatment
Trimethoprim		antibacterial
Trimethoprim/sulfa		antibacterial
Piritrexim	Burroughs Wellcome (Rsch. Triangle Park, NC)	PCP treatment

Drug Name	Manufacturer	Indication
Pentamidine isethionate for inhalation	Fisons Corporation (Bedford, MA)	PCP prophylaxis
Spiramycin	Rhone-Poulenc Pharmaceuticals (Princeton, NJ)	cryptosporidial diarrhea
Intraconazole-R51211	Janssen Pharm, (Piscataway, NJ)	histoplasmosis; cryptococcal meningitis
Trimetrexate	Warner-Lambert	PCP

OTHER

Drug Name	Manufacturer	Indication
Recombinant Human Erythropoietin	Ortho Pharm. Corp. (Raritan, NJ)	severe anemia assoc. with AZT therapy
Megestrol Acetate	Bristol-Myers (New York, NY)	treatment of anorexia assoc. w/AIDS
Total Enteral Nutrition	Norwich Eaton Pharmaceuticals (New York, NY)	diarrhea and malabsorption related to AIDS

It will be understood that the scope of combinations of the compounds of this invention with AIDS antivirals, immunomodulators, anti-infectives or vaccines is not limited to the list in the above Table,

but includes in principle any combination with any pharmaceutical composition useful for the treatment of AIDS.

Certain compounds of Table C are the following: L-697,661 or '661' is 3-([4,7-dichloro-1,3-benzoxazol-2-yl)methyl]-amino)-5-ethyl-6-methyl-pyridin-2(1H)-one; L-696,229 is 3-[2-(1,3-benzoxazol-2-yl)-ethyl]-5-ethyl-6-methyl-pyridin-2(1H)-one. The synthesis of L-697,661 and L-696,229 is described in EPO 484071, and EPO 462800, both herein incorporated by reference. The synthesis of ddC, ddI and AZT are also described in EPO 484071.

Preferred combinations are simultaneous, intermittent, or alternating treatments of an inhibitor of HIV protease and a non-nucleoside inhibitor of HIV reverse transcriptase. An optional third component in the combination is a nucleoside inhibitor of HIV reverse transcriptase, such as AZT, ddC or ddI. Preferred inhibitors of HIV protease are L-739,684 (Compound B) or L-739,594 (Compound C). Preferred non-nucleoside inhibitors of HIV reverse transcriptase include L-697,661. These combinations may have synergistic effects on limiting the spread of HIV. Preferred combinations include the following (1) L-739,684 or L-739,594, with L-697,661, and, optionally, AZT or ddI or ddC; (2) L-739,594 or L-739,684, and any of AZT or ddI or ddC.

EXAMPLE 1

Preparation of cis-N-tert-butyl-decahydro-(4aS,8aS)-isoquinoline-3(S)-carboxamide, Compound 5

Step 1: Preparation of cis-N-tert-butoxycarbonyl-2carboxy-decahydro-isoquinoline

A suspension of L-3-carboxy-1,2,3,4-tetrahydroiso-quinoline, 21.3 g, prepared as described by G.E. Hein, et al., J. Am. Chem. Soc., 84, 4487 (1962), in 650 mL of ethanol and 650 mL of water was shaken with 21.3 g of 5% rhodium on carbon under 15 atm of hydrogen at 50°C until 3 molar equivalents of hydrogen were

consumed (6h). After cooling the catalyst was filtered off and the solvents removed under reduced pressure. After drying, the residue was recrystallized from ethanol affording 8 g of L-cis-3-carboxydecahydro-isoquinoline. To a solution of 5 g of L-cis-3-carboxydecahydroso-quinoline in 75 mL of dioxane and 185 mL of dilute sodium carbonate (pH8) was added 7 g of di-tert-butyldicarbonate. After 2 days stirring at room temperature, the mixture was acidified with 1N HCl until pH is 3 and extracted with three 100 mL portions of ethyl acetate. After concentration and drying there was obtained 4.1 g of a white solid.

Step 2: Preparation of cis-N-tert-butyl-decahydro (4aS,8aS)-isoquinoline-3(S)-carboxamide

To a stirred solution of cis-N-tert-butoxycarbonyl-3-carboxydecahydro-isoquinoline (the product of Step 1), 4.1 g, in 100 mL of tetrahydrofuran cooled to -20°C was added 2.8 mL of N-methylmorpholine and 2.42 mL of isobutylchloroformate. After 15 min, 2.4 mL of tert-butylamine was added and the mixture allowed to warm to room temperature and stir overnight. The mixture was diluted with 200 mL of ethyl acetate and 100 mL of 10% citric acid. The organic layer was washed with saturated sodium bicarbonate, dried ($MgSO_4$) and concentrated. The resulting white solid was dissolved in 50 mL of ice cold methylene chloride and 25 mL of trifluoroacetic acid. After warming and stirring for 2 h, the solvents were removed under reduced pressure. The residue was dissolved in 100 mL of methylene chloride, washed with 50 mL of saturated sodium bicarbonate, dried and concentrated. The product, 3.0 g, solidified on standing.

EXAMPLE 2

Preparation of 3(S)-azido-(1,2R)-epoxy-4-phenyl-butane, Compound 10

A quantity of CuCN, 2.43 g, was added to a solution of butadiene monooxide, 19 g, in 500 mL anhydrous tetrahydrofuran and the mixture was cooled to -78°C. Phenyl magnesium bromide solution in ether, 32 mmol, was added dropwise to this mixture. The reaction

mixture was warmed to 0°C and was stirred until the reaction became homogeneous. The reaction mixture was cooled to -78°C and 0.29 mole of phenylmagnesium bromide solution in ether was added dropwise for 30 min. The reaction mixture was allowed to warm to room temperature with stirring then quenched by slow addition of saturated NH_4Cl (50 mL) followed by NH_4OH (30 mL), saturated NH_4Cl (200 mL) and H_2O (100 mL). Aqueous layer was extracted with two 200 mL portions of ethyl acetate. Combined organic layers were dried and concentrated. The residue was distilled under vacuum (0.1 torr) at 100°C to give trans-4-phenyl-2-butene-1-ol (38.9 g, 79% pure).

A mixture of powdered 4Å molecular sieves, 3 g, titanium tetraisopropoxide, 1.5 mL, and diethyl D-tartrate, 1.1 mL, in anhydrous methylene chloride (350 mL) was cooled to -20°C and tert-butyl-hydroperoxide solution in isooctane, 210 mmol, was added slowly with stirring. After 30 minutes at -20°C a solution of trans-4-phenyl-2-butene-1-ol, 15.3 g, in anhydrous methylene chloride (50 mL) was added dropwise for 20 min at -20°C. The reaction mixture was aged at -20°C in a freezer for 20 hours. Water (40 mL) was added to the reaction mixture and after 30 minutes at 0°C, 30% NaOH in brine (6 mL) was added. The resulting mixture was stirred for 1 h at room temperature. The organic phase was separated and the aqueous layer was extracted with two 30 mL portions of methylene chloride. Combined organic layers were dried over Na_2SO_4, diluted with toluene (300 mL) and concentrated. Chromatography on silica gel with 40% ethyl acetate in hexane gave (2R, 3R)-epoxy-4-phenylbutan-1-ol (10.3 g).

A solution of titanium tetraisopropoxide, 5.6 mL, and azidotrimethylsilane, 5.0 mL, in anhydrous benzene (100 mL) was refluxed for 5 h. To this refluxing mixture was added a solution of (2R, 3R)-epoxy-4-phenylbutan-1-ol, 2.6 g, in anhydrous benzene (10 mL). The reaction mixture was refluxed for 15 min, cooled to room temperature and quenched by addition of 5% H_2SO_4 (150 mL). After stirring the resulting biphasic mixture for 1 h, the organic layer was separated and the aqueous layer was extracted with two 20 mL portions

of ethyl acetate. Combined organic layers were washed with saturated sodium bicarbonate (50 mL), dried over $MgSO_4$ and concentrated. The oily azidodiol product was dissolved in chloroform (30 mL) and 2-acetoxyisobutyryl chloride, 2.5 mL, was added. After stirring for 5 h at room temperature, saturated sodium bicarbonate (50 mL) was added and the resulting biphasic mixture was stirred for 10 min. The aqueous layer was extracted with two 30 mL portions of chloroform. Combined organic layers were dried over Na_2SO_4 and concentrated. The residue was dissolved in anhydrous tetrahydrofuran (10 mL) and solid NaOMe, 0.614 g, was added. After stirring for 3 h at room temperature, saturated NH4Cl (20 mL) was added and the mixture extracted with two 20 mL portions of ethyl acetate. Combined organic layers were dried over $MgSO_4$ and concentrated. Chromatography on silica gel with 8% ethyl acetate in hexanes gave 3(S)-azido-(1, 2R)-epoxy-4-phenylbutane (1.32 g) as an oil.

EXAMPLE 3

Preparation of cis-N-tert-butyl-decahydro-2[2(R)-hydroxy-4-phenyl-3(S)-azidobutyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide, Compound 11

A mixture of 6.46 g of cis-N-tert-butyl-decahydro-(4aS,8aS)-isoquinoline-3(S)-carboxamide (product of Example 1) and 10.3 g of 3(S)-azido-(1,2R)-epoxy-4-phenylbutane (product of Example 2) in 200 mL of isopropanol was heated to 80°C overnight then concentrated to dryness under reduced pressure. Recrystallization from ethyl acetate-hexanes gave 9.63 g of product of melting point 149-50°C.

EXAMPLE 4

Preparation of cis-N-tert-butyl-decahydro-2[2(R)-hydroxy-4-phenyl-3(S)-aminobutyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide, Compound 12

A solution of 5.0 g of cis-N-tert-butyl-decahydro-2[2(R)-hydroxy-4-phenyl-3(S)-azidobutyl](4aS,8aS)-isoquinoline-3(S)-carboxamide (product of Example 3) in 200 mL of tetrahydrofuran and 50 mL of methanol was shaken with 1 g of 10% palladium on carbon catalyst under an atmosphere of hydrogen for 48 h. Removal of the catalyst by filtration and concentration under reduced pressure gave 4.68 g of product as a white solid of melting point 165-166°C.

EXAMPLE 5

Preparation of 3(S)-tetrahydrofuranyl succinimidyl carbonate, Compound 13

A solution of 20 mL of 12.5% phosgene in toluene and 1.0 g of (S)-(+)-3-hydroxytetrahydrofuran was aged in a stoppered flask for 48 hours. The solvents were removed under reduced pressure and the residue dissolved in 30 mL of anhydrous acetonitrile, then cooled in an ice bath. To this cold solution was added 1.7 g of N-hydroxy-succinimide and 1.9 mL of triethylamine. The mixture was aged for 12 hours at 25°C, then concentrated to dryness. The residue was dissolved in 200 mL of ethyl acetate, washed with 2 x 50 mL of water, dried over $MgSO_4$ and concentrated to dryness under reduced pressure. The oily residue was dissolved in 10 mL of ethyl acetate passed through a 300 mL of silica gel, eluting with ethyl acetate. Concentration of the eluate to dryness gave 2 g of product as a white crystalline solid.

EXAMPLE 6

Preparation of hexahydrofuro[2,3b]furan-3a-ol

To a stirred solution of 10 g of 2-n-butyloxy-3-allyl-tetrahydrofuran-3-ol (prepared as described by M. Jalali-Naini and J.Y. Lallemand, Tetrahedron Letters, pp 497-500, 1986) in 10 mL of methanol and 220 mL of methylene chloride cooled to -78°C was added a stream of ozone until a blue color persisted. The mixture was purged with nitrogen, warmed to 0°C and diluted with 100 mL of ethanol. To this mixture was added 5 g of $NaBH_4$. After aging at 25°C for 6 hours, the solvents were removed under reduced pressure and the residue partitioned between 50 mL of 10% citric acid and 3 x 100 mL of methylene chloride. The organic extracts were dried over $MgSO_4$ and concentrated to ca. 200 mL. To this stirred solution was added 0.10 g of p-toluenesulfonic acid monohydrate. The mixture was heated at reflux for 24 hours, then concentrated to dryness under reduced pressure. Evaporative distillation of the residue at 0.1 mm (110-130°C) gave 2 g of the title compound.

EXAMPLE 7

Preparation of tertiary alcohol urethanes

Step A: Preparation of hexahydrofuro[2,3b]furan-3a-yl-succinimidyl carbonate

To a stirred solution of 1 g of hexahydrofuro[2,3b]furan-3a-ol in 25 mL of 12.5% phosgene in toluene cooled to -10°C was added 1 mL of pyridine. The mixture was allowed to warm to 25°C and stir for 4 hours, then concentrated to dryness under reduced pressure. The oily residue after drying under vacuum (1.3 g) was dissolved in 30 mL of anhydrous acetonitrile, then cooled in an ice bath. To this cold solution was added 1.14 g of N-hydroxysuccinimide and 1.3 mL of triethylamine. The mixture was aged for 48 hours at 25°C, then concentrated to dryness. The residue was dissolved in 200 mL of ethyl

acetate, washed with 2 x 50 mL of water, dried over $MgSO_4$ and concentrated to dryness under reduced pressure. Chromatography of the residue with 20% ethyl acetate in methylene chloride gave 0.49 g of product as a white crystalline solid.

Step B: Preparation of N-(2(R)-hydroxy-1(S)-indanyl)-5(S)-(hexahydrofuro[2,3b]-furanyl-3a-oxycarbonylamino)-4(S)-hydroxy-6-phenyl-2(R)-(4-(2-(4-morpholinyl)ethoxy)-phenyl)methyl hexanamide

To a stirred suspension of 100 mg of the product of Example 4 in 15 mL of methylene chloride was added 90 mg of hexahydrofuro[2,3b]furan-3a-yl succinimidyl carbonate and 0.060 mL of triethyl amine. After stirring for 12 hours, the mixture was diluted with 50 mL of chloroform, washed with 10 mL of sat'd. sodium bicarbonate, and concentrated to dryness. Chromatography using 8% MeOH in $CHCl_3$ gave 80 mg of product as a white crystalline solid.
Calc'd for $C_{41}H_{51}N_3O_9$

C, 67.47 H, 7.07 N, 5.76

Found: C, 67.45 H, 6.90 N, 5.77.

EXAMPLE 8

Preparation of (3R, 3aS, 6aR)-3-hydroxyhexahydrofuro[2,3-b]furan:

Step A: (2R,3S,1'R) and (2R,3S,1'S) Methyl 2-(1'-tetrahydro-pyranyloxy)-3-allyl-succinate

A solution of 7.2 g of (-)-dimethyl (2R,3S)-3-allyl-2-hydroxysuccinate (prepared using the procedure described by D. Seebach, J. Aebi and D. Wasmuth, Organic Syntheses, 1985, 63, 109-120), 250 mg of p-toluenesulfonic acid monohydrate and 9.8 mL of dihydropyran in 100 mL of anhydrous diethyl ether was stirred for 12 hours, washed with saturated aqueous $NaHCO_3$ (1x) and brine (1x). The organic layer was dried over Na_2SO_4 and filtered; the evaporation of the solvents gave 9.5 g of the title compound as an oil.

Step B: (2R,3R,1'R) and (2R,3R,1'S) (1'-tetrahydropyranyloxy)-3-allyl-butane-1,4-diol

A solution of 9.4 g of (2R,3S,1'R) and (2R,3S,1'R) methyl 2-(1'-tetrahydropyranyloxy)-3-allyl-succinate in 15 mL diethyl ether was added dropwise to a suspension of 3.1 g of $LiAlH_4$ in 70 mL ether cooled to 0°C. After 12 hours, the mixture was heated to reflux for 1 hour and then cooled to 0°C. The reaction was quenched by sequential dropwise addition of 3.1 mL of water, 3.1 mL 20% aqueous NaOH and 8 mL of water . The cooling bath was removed and after stirring for 1 hour, 50 mL of THF was added. After 30 min., Na_2SO_4 was added and the mixture was filtered through celite, washing the filter cake with THF. Evaporation of the solvents gave 6.3 g of the title compound as a clear, colorless oil.

Step C: (2R,3R) 1,2-O-isopropylidene-3-allyl butane-1,4-diol

A solution of 6.3 g of (2R,3R,1'R) and (2R,3R,1'R) (1'-tetrahydropyranyloxy)-3-allyl-butane-1,4-diol and 400 mg of p-toluenesulfonic acid monohydrate in 100 ml of methanol was stirred for 1 hour at 24°C, then concentrated under reduced pressure. The crude triol product was taken up in 500 mL of acetone with 150 mg of p-toluenesulfonic acid monohydrate and stirred at 24°C for 2.5 hours. Concentration under reduced pressure gave a residue which was taken up in ethyl acetate and washed with saturated aqueous $NaHCO_3$. The layers were separated and the organic layer was dried over Na_2SO_4. After filtration and evaporation of the solvent, purification of the residue by chromatography over silica gel (50% ethyl acetate/hexanes) gave 4.1 g of the title compound as a colorless oil.

Step D: (2R,3S,4R) and (2S,3S,4R) 2-methoxy-3-allyl-4-hydroxytetrahydrofuran

To a stirred solution of 0.55 mL oxalyl chloride in 20 mL CH_2Cl_2 cooled to -50°C was added 1.03 mL dimethyl sulfoxide dissolved in 2 mL CH_2Cl_2 dropwise, maintaining the temperature between -40°C and -50°C. After stirring for 3 min at -50°C, a solution

of 1.0 g of (2R, 3R) 1,2-O-isopropylidene-3-allyl-butane-1,4-diol in 3 mL CH_2Cl_2 was added dropwise over 5 min, the solution was allowed to warm to -20°C over 1.5 hours. After addition of 5 mL of triethylamine the mixture was allowed to warm further to 24°C, then 15 mL of water was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (2x10 ml) and the combined organic layers were dried over Na_2SO_4. After filtration and concentration under reduced pressure, purification of the residue by chromatography over silica gel (25% ethyl acetate/ hexanes) gave 780 mg of the aldehyde intermediate as a colorless oil. A solution of 1.3 g of the aldehyde, 300 mg camphorsulfonic acid and 25 mL methanol was stirred at 24°C for 12 hours. The reaction mixture was quenched by addition of 5 mL saturated aqueous $NaHCO_3$, stirred for 10 min, then concentrated under reduced pressure. The residue was taken up in ethyl acetate, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. Purification of the residue (a mixture of three compounds) by chromatography over silica gel gave, in order of elution, 225 mgs of product isomer A as an oil, 180 mgs of an impurity, and 590 mgs of product isomer C as an oil. Product isomers A and C were combined for the next step.

Step E: (3R, 3aS, 6aR) 3-hydroxyhexahydrofuro[2,3-b]furan

A solution of 500 mg (2R, 3S, 4R) and (2S, 3S, 4R) 2-methoxy-3-allyl-4-hydroxytetrahydrofuran in 25 mL methanol and 25 mL methylene chloride cooled to -78°C was saturated with ozone for 1 hour. Nitrogen was bubbled through the solution for 5 min. and the ozonide was quenched with 3 ml of methyl sulfide. The cooling bath was removed and the mixture was warmed to 24°C. Evaporation of the solvent gave the crude aldehyde as a clear, colorless oil. The aldehyde was taken up in 20 mL absolute ethanol, cooled to 0°C and 0.18 g of $NaBH_4$ was added in three portions with stirring over 10 min. After 15 min. the reaction was quenched with 3 mL 10% aqueous citric acid and concentrated. The residue was taken up in ethyl acetate and dried over Na_2SO_4, filtered and concentrated under reduced pressure.

Purification of the residue by chromatography over silica gel (75% ethyl acetate/hexanes) gave 430 mg of (2R,3S,4R) and (2S,3S,4R) 2-methoxy-3-(2'-hydroxyethyl)-4-hydroxytetrahydrofuran as a clear, colorless oil. A solution of 200 mg of camphorsulfonic acid and 400 mg of (2R,3S,4R) and (2S,3S,4R) 2-methoxy-3-(2'-hydroxyethyl)-4-hydroxytetrahydrofuran in 100 mL of dry CH_2Cl_2 was stirred at 24°C for 12 hours. The reaction was quenched by additon of 5 mL of saturated aqueous $NaHCO_3$. After stirring for 10 minutes, the layers were separated and the aqueous layer was extracted with ethyl acetate (3x 30 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by chromatography over silica gel (75% ethyl acetate/hexanes) gave 350 mg of the title compound as a clear, colorless oil.

EXAMPLE 9

Preparation of (3R, 3aS, 6aR) 3-hydroxyhexahydrofuro[2,3-b]furanyl 2-pyridyl carbonate

A mixture of 380 mg of [3R, 3aS, 6aR]-3-hydroxyhexahydrofuro[2,3-b]furan, 950 mg di(2-pyridyl) carbonate and 0.620 mL triethylamine in 20 mL of dry CH_2Cl_2 was stirred at 24°C for 12 hours, diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ (1x15 mL), brine (1x15 mL) and dried over Na_2SO_4. After filtration and concentration under reduced pressure, purification of the residue by chromatography over silica gel (75% ethyl acetate/ hexanes) gave 460 mg of (3R, 3aS, 6aR) 3-hydroxyhexahydrofuro[2,3-b]furanyl 2-pyridyl carbonate as a tan oil. Unreacted starting alcohol, 120 mg, was also recovered.

EXAMPLE 10

Preparation of (3S,4aS,8aS,2'R,3'S,3"R,3"aS,6"aR) N-tert-butyl 2(2'-hydroxy-4'-phenyl-3'(3"-hexahydrofuro[2,3-b]furanyloxycarbonyl-amino)butyl)-decahydroisoquinoline-3-carboxamide (Compound C) (L-739,594)

A mixture of 400 mg of (3R, 3aS, 6aR) 3-hydroxy-hexahydrofuro[2,3-b]furanyl 2-pyridyl carbonate and 630 mg of (3S,4aS,8aS,2'R,3'S) N-tert-butyl 2(2'-hydroxy-4'-phenyl-3'-aminobutyl)-decahydroisoquinoline-3-carboxamide in 30 mL of dry CH_2Cl_2 was stirred at 24°C for 12 hours, diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ (1x20 mL), brine (1x15 mL) and dried over Na_2SO_4. After filtration and concentration under reduced pressure, purification of the residue by chromatography over silica gel (75% ethyl acetate/ hexanes) gave 620 mg of the title compound as a white crystalline solid m.p. 98-101°C; ^{1}H-NMR ($CDCl_3$) δ 1.35 (s, 9H), 1.4-1.9 (br m 14H), 2.25 (br d, 2H), 2.5-2.7 (br m, 2H), 2.8-3.0 (br m, 4H), 3.1-3.2 (t, 1H), 3.7 (m, 2H), 3.75-3.95 (br m, 3H), 4.05 (br m 1H), 5.0 (br q, 1H), 5.59 (d, 1H), 5.61 (d, 1H), 5.77 (s, 1H), 7.18-7.3 (br n, 5H);

Elemental analysis, calc'd. for $C_{31}H_{47}N_3O_6$ (557.73):

	C, 66.76;	H, 8.49;	N, 7.53
Found:	C, 66.34;	H, 8.54;	N, 7.65.

(3S, 3aR, 6aS)-3-Hydroxyhexahydrofuro[2,3-b]furan From (+)-diethyl (2S,3R)-3-allyl-2-hydroxysuccinate using the procedure substantially as described above for preparation of (3R, 3aS, 6aR)-3-hydroxyhexa-hydrofuro[2,3-b]furan there was obtained a clear colorless oil.

EXAMPLE 11

Preparation of (3S,4aS,8aS,2'R,3'S,3"S,3"aR,6"aS) N-tert-Butyl 2(2'-hydroxy-4'-phenyl-3'(3"-hexahydrofuro[2,3-b]furanyloxycarbonyl-amino)butyl)-decahydroisoquinoline-3-carboxamide (L-739,663)

From (3S, 3aR, 6aS) 3-hydroxy-hexahydrofuro[2,3-b]furan using the procedure substantially as described above for preparation of Compound C there was obtained a white solid: m.p. 85-9°C; Elemental analysis, calc'd. for $C_{32}H_{49}N_3O_6$ x 0.40 $CHCl_3$ (605.489):

	C, 62.28;	H, 7.69;	N, 6.94
Found:	C, 62.30;	H, 7.30;	N, 7.00.

EXAMPLE 12

Preparation of (3R, 3aS, 7aR) 3-hydroxy-hexahydrofuro[2,3-b]pyran:

Step A: (2R, 3S, 4R) and (2S, 3S, 4R) 2-methoxy-3-(3'-hydroxypropyl)-4-hydroxytetrahydrofuran

To a stirred solution of 225 mg (2R, 3S, 4R) and (2S, 3S, 4R) 2-methoxy-3-allyl-4-hydroxytetrahydrofuran in 5 mL of THF cooled to -10°C was added dropwise 4.3 mL of 0.5 M 9-BBN in THF. After stirring at 24°C for 12 hours, another 2.5 mL of 0.5 M 9-BBN was added and stirring was continued for 24 hours. The reaction was quenched with a mixture of 1 mL of 30% H_2O_2 and 1 mL of 20% NaOH. The resulting mixture was heated to 50°C for 1.5 hours and then cooled to 24°C and extracted with 3 portions of ethyl acetate. After drying over Na_2SO_4 , concentration under reduced pressure, and purification of the residue by chromatography over silica gel (75% ethyl acetate/hexanes) to afford 140 mg of the title compound as a clear colorless oil.

Step B: (3R, 3aS, 7aR) 3-hydroxyhexahydrofuro[2,3-b]pyran

A solution of 140 mg of (2R, 3S, 4R) and (2S, 3S, 4R) 2-methoxy-3-(3'-hydroxypropyl)-4-hydroxytetrahydrofuran and 100 mg camphorsulfonic acid in 100 mL CH_2Cl_2, was stirred at 24°C for 12 hours. The reaction mixture was quenched with 3 mL of saturated aqueous $NaHCO_3$ stirred for 10 minutes. The layers were separated and the aqueous layer was extracted with ethyl acetate (3x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and

concentrated under reduced pressure. Purification of the residue by chromatography over silica gel (75% ethyl acetate/hexanes) to afford 100 mg of the title compound as a clear, colorless oil.

EXAMPLE 13

(3S,4aS,8aS,2'R,3'S,3"R,3"aS,7"aR) N-tert-Butyl 2(2'-hydroxy-4'-phenyl-3'(3"-hexahydro-4"H-furo[2,3-b]pyranyloxycarbonylamino)-butyl)-decahydroisoquinoline-3-carboxamide (L-739,761)

From (3R, 3aS, 7aR) 3-hydroxy-4H-hexahydrofuro[2,3-b]pyran using the procedure substantially as described above for preparation of Compound C there was obtained a white solid: m.p. 147-53°C; Elemental analysis, calc'd. for $C_{32}H_{49}N_3O_6 \times 1.25\ CHCl_3$ (720.988):

	C, 55.39;	H, 7.03;	N, 5.83
Found:	C, 55.44;	H, 6.99;	N, 5.93.

Preparation of (3S, 3aR, 7aS) 3-hydroxy-hexahydrofuro[2,3-b]pyran From (+)-diethyl (2S,3R)-3-allyl-2-hydroxysuccinate using the procedure substantially as described above for preparation of (3R, 3aS, 7aR) 3-hydroxy-4H-hexahydrofuro[2,3-b]pyran there was obtained a clear colorless oil.

EXAMPLE 14

(3S,4aS,8aS,2'R,3'S,3"S,3"aR,7"aS) N-tert-Butyl 2(2'-hydroxy-4'-phenyl-3'(3"-hexahydro-4"H-furo[2,3-b]pyranyloxycarbonyl-amino)butyl)-decahydroisoquinoline-3-carboxamide (Compound B) (L-739,684)

From (3S, 3aR, 7aS) 3-hydroxy-4H-hexahydrofuro[2,3-b]pyran using the procedure substantially as described above for preparation of Compound C there was obtained a white solid: m.p. 82-6°C; Elemental analysis, calc'd. for $C_{32}H_{49}N_3O_6$ (571.76):

	C, 67.22;	H, 8.64;	N, 7.35
Found:	C, 67.22;	H, 8.73;	N, 7.42.

EXAMPLE 15

Preparation of (3R, 3aS, 5S, 6aR) and (3R, 3aS, 5R, 6aR) 3-hydroxy-5-methyl-hexahydrofuro[2,3-b]furan:

Step A: (1S, 3S, 4R,1'R,2"SR), (1S, 3S, 4R,1'S,2"SR), (1S, 3S, 4R,1'R,2"SR) and (1R, 3S, 4R,1'S,2"SR) 2-Methoxy-3-(1'-oxiranylmethyl)-4-(2"-tetrahydropyranyloxy)tetrahydrofuran

A mixture of 0.5 g (3.2 mmole) of (2R,3S,4R) and (2S,3S,4R) 2-methoxy-3-allyl-4-hydroxytetrahydrofuran, 0.87 mL (9.6 mmole) of dihydropyran and 10 mg of p-toluensulfonic acid in 25 mL of ether was stirred at 24°C for 12 h. The resulting solution was washed with 20 mL of sat'd $NaHCO_3$, 10 mL of brine, dried over Na_2SO_4 and concentrated. Chromatography of the residue over silica gel using 50% ethyl acetate in hexanes gave 625 mg of the tetrahydropyranyl ether as an oil. A solution of the tetrahydropyranyl ether (300 mg) and 461 mg of mCPBA (60%, 1.6 mmole) in 25 mL of CH_2Cl_2 was stirred at 24°C for 12 h. The solution was washed with 15 mL of sat'd $NaHCO_3$, dried over Na_2SO_4 and concentrated. Chromatography of the residue over silica gel using 50% ethyl acetate in hexanes gave 238 mg of the epoxy-THP ether as an oil.

Step B: (2R,3S,4R,2'SR, 2"SR) 2-methoxy-3-(2'-hydroxypropyl)-4-(2"-tetrahydropyranyloxy)tetrahydrofuran

To a stirred, ice cold suspension of 50 mg (1.4 mmole) of $LiAlH_4$ in 10 mL of THF was added 230 mg of the epoxy-THP ether

(product of Step A). After warming to 24°C and stirring for 12 h, the reaction was quenched with 0.1 mL of water, 0.1 mL of 20% NaOH, stirred for 30 min then filtered through diatomaceous earth. Chromatography of the residue after concentration of the filtrate using 75% ethyl acetate in hexanes gave 180 mg of product as an oil.

Step C: (3R, 3aS, 5S, 6aR) and (3R, 3aS, 5R, 6aR) 3-hydroxy-5-methyl-hexahydrofuro[2,3-b]furan

A solution of 180 mg of (2R,3S,4R,2'SR, 2"SR) 2-methoxy-3-(2'-hydroxypropyl)-4-(2"-tetrahydropyranyloxy)-tetrahydrofuran (product of Step B), 50 mg of camphorsulfonic acid and 5 mL of methanol in 50 mL of CH_2Cl_2 was stirred at 24°C for 14 h. The mixture was concentrated to dryness, redissolved in 70 mL of CH_2Cl_2 and stirred for an additional 12 h. The solution was washed with 3 mL of sat'd $NaHCO_3$, dried over Na_2SO_4 and concentrated. Chromatography of the residue over silica gel using 75% ethyl acetate in hexanes gave 60 mg of (3R, 3aS, 5R, 6aR) 3-hydroxy-5-methyl-hexahydrofuro[2,3-b]furan (isomer A) and 60 mg of (3R, 3aS, 5S, 6aR) 3-hydroxy-5-methyl-hexahydrofuro[2,3-b]furan (isomer B) as oils.

EXAMPLE 16

(3S,4aS,8aS,2'R,3'S,3"R,3"aS,5"R,6"aR) N-tert-butyl 2(2'-hydroxy-4'-phenyl-3'(5"-methyl-3"-hexahydrofuro[2,3-b]furanyloxycarbonyl-amino)butyl)-decahydroisoquinoline-3-carboxamide (L-739,783)

From (3R, 3aS, 5R, 6aR) 3-hydroxy-5-methyl-hexahydrofuro[2,3-b]furan using the procedure substantially as described above for preparation of Compound C there was obtained a white solid: m.p. 100-102°C; Elemental analysis, calc'd. for $C_{33}H_{51}N_3O_6$ x 0.35 $CHCl_3$ (571.76):

	C, 63.32;	H, 8.11;	N, 6.95
Found:	C, 63.21;	H, 7.90;	N, 7.29.

EXAMPLE 17

(3S,4aS,8aS,2'R,3'S,3"R,3"aS,5"S,6"aR) N-tert-butyl 2(2'-hydroxy-4'-phenyl-3'(5"-methyl-3"-hexahydrofuro[2,3-b]furanyloxycarbonyl-amino)butyl)-decahydroisoquinoline-3-carboxamide (L-743,768)

From (3R, 3aS, 5S, 6aR) 3-hydroxy-5-methyl-hexahydrofuro[2,3-b]furan using the procedure substantially as described above for preparation of Compound C there was obtained a white solid: m.p. 105-7°C; Elemental analysis, calc'd. for $C_{33}H_{51}N_3O_6$ x 0.10 $CHCl_3$ (583.703):

	C, 66.05;	H, 8.48;	N, 7.20
Found:	C, 66.21;	H, 8.09;	N, 7.04.

EXAMPLE 18

Preparation of (2S, 3S, 3aR, 7aS), (2R, 3R, 3aS, 7aR) and (2R, 3S, 3aR, 7aS), (2S, 3R, 3aS, 7aR) 3-hydroxy-2-methyl-4H-hexahydrofuro[2,3-b]pyran:

Step A: trans-2(2'-methyl-3'-propynyl-1'-oxy)-3-iodotetrahydropyran

To a stirred, ice cold suspension of 16 g (71 mmole) of N-iodosuccinimide100 mL of CH_2Cl_2 was added a solution of 5 g (71 mmole) of dihydropyran and 7.6 g (109 mmole) of 3-butyn-2-ol in 100 mL of CH_2Cl_2 over 20 min. After warming to 24°C with stirring over 2h, 200 mL of water were added and the stirring continued for 1h. The layers were separated and the aqueous layer extracted 2x50 mL of CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. Chromatography over silica gel using 30% ethyl acetate in hexane gave 16.4 g of the iodo ether as an oil.

Step B: (2S, 3aR, 7aS), (2R, 3aS, 7aR), (2R, 3aR, 7aS) and (2S, 3aS, 7aR) 3-methylene-2-methyl-4H-hexahydrofuro[2,3-b]pyran

To a refluxing solution of 20.7 mL (77 mmole) tri n-butyltinhydride in 100 mL of toluene was added 100 mg of AIBN followed by a solution of 16.4 g (64 mmole) of *trans* -2(2'-methyl-3'-propynyl-1'-oxy)-3-iodotetrahydropyran, dropwise over 1 h. After 12 h at reflux, the mixture was cooled to 24°C and concentrated. The residue was partitioned between petroleum ether and acetonitrile (200 mL of each) and the acetonitrile (lower) layer was concentrated. Purification by chromatography on silica gel, eluting with 10% ethyl acetate in hexane, gave 8 g (81%) of product as an oil.

Step C: (2S, 3S, 3aR, 7aS), (2R, 3R, 3aS, 7aR) and (2R, 3S, 3aR, 7aS), (2S, 3R, 3aS, 7aR) 3-hydroxy-2-methyl-4H-hexahydrofuro[2,3-b]pyran

A stream of ozone was dispersed into a solution of (2S, 3aR, 7aS), (2R, 3aS, 7aR), (2R, 3aR, 7aS) and (2S, 3aS, 7aR) 3-methylene-2-methyl-4H-hexahydrofuro[2,3-b]pyran at -78°C in 150 mL of methanol and 150 mL of CH_2Cl_2 for 30 min. The resulting blue solution was purged with nitrogen until colorless, then quenched by addition of 20 mL of dimethyl sulfide. Concentration under reduced pressure gave 12 g of crude ketone. To a solution of 6 g of the crude ketone in 250 mL of CH_2Cl_2 , cooled to -78°C was added dropwise 57 mL of 1.0 M diisobutylaluminumhydride in hexane. After stirring for an additional 2 h at -78°C, 100 mL of saturated sodium potassium tartrate and 200 mL of CH_2Cl_2 were added and the mixture allowed to warm to 24°C. The organic layer was separated, dried (Na_2SO_4) and concentrated. Chromatography of the residue on silica gel with 30% ethyl acetate in hexane gave 1.02 g of product isomer A (higher Rf) and 1.15 g (lower Rf) of product isomer B.

EXAMPLE 19

(3S,4aS,8aS,2'R,3'S,2"S,3"S,3"aR,7"aS) and
(3S,4aS,8aS,2'R,3'S,2"R,3"R,3"aS,7"aR) N-tert-Butyl 2(2'-hydroxy-4'-

phenyl-3'(2"-methyl-3"-hexahydro-4"H-furo[2,3-b]pyranyloxycarbonyl-amino)butyl)-decahydroisoquinoline-3-carboxamide (L-743,787)

From (2S, 3S, 3aR, 7aS) and (2R, 3R, 3aS, 7aR) 3-hydroxy-2-methyl-4H-hexahydrofuro[2,3-b]pyran (isomer A) using the procedure substantially as described above for preparation of Compound C there was obtained a white solid: m.p. 91-2°C; Elemental analysis, calc'd. for $C_{33}H_{51}N_3O_6$ (585.792):

	C, 67.66;	H, 8.78;	N, 7.17
Found:	C, 68.05;	H, 8.80;	N, 6.96.

EXAMPLE 20

(3S,4aS,8aS,2'R,3'S,2"R,3"S,3"aR,7"aS) and (3S,4aS,8aS,2'R,3'S,2"S,3"R,3"aS,7"aR) N-tert-Butyl 2(2'-hydroxy-4'-phenyl-3'(2"-methyl-3"-hexahydro-4"H-furo[2,3-b]pyranyloxycarbonyl-amino)butyl)-decahydroisoquinoline-3-carboxamide (L-743,788)

From (2R, 3S, 3aR, 7aS) and (2S, 3R, 3aS, 7aR) 3-hydroxy-2-methyl-4H-hexahydrofuro[2,3-b]pyran (isomer B) using the procedure substantially as described above for preparation of Compound C there was obtained a white solid: m.p. 89-90°C; Elemental analysis, calc'd. for $C_{33}H_{51}N_3O_6 \times 0.35\ C_6H_6$ (613.132):

	C, 68.75;	H, 8.73;	N, 6.85
Found:	C, 68.68;	H, 9.00;	N, 6.49.

EXAMPLE 21

Preparation of (3S,4aS,7aS,2'R,3'S,3"S,3"aR,7"aS) N-tert-butyl-octahydro-2(2'-hydroxy-4'-phenyl-3'(3"-hexahydro-4"H-furo[2,3-b]pyranyloxycarbonyl-amino)butyl)-1H-pyrindene-3-carboxamide (L-743,639)

Step A: (1S, 2R) 1-Methyl hydrogen cyclopentanedicarboxylate

A mixture of 40 g of *cis*-cyclopentane 1,2-dicarboxylic acid anhydride and 300 mL of methanol was refluxed for 3 h, then

concentrated and dried under vacuum. The resulting monoester, 50 g, was dissolved in 100 mL of ethyl acetate and a solution of 50 g of (+)-ephedrine hemihydrate in 250 mL of hot ethyl acetate was added. On cooling and standing for 24 h, 40 g of white crytals were formed. The resolved monoester was liberated by dissolving the salt in 100 mL of 2N sulfuric acid and extracting with 3 X 300 mL of ethyl acetate. After drying, 20.5 g of resolved monoester was obtained: $[\alpha]_D^{25} = +5^o$ (c=1.4 MeOH).

Step B: (1S, 2R) Methyl 2-formylcyclopentanecarboxylate

A solution of (1S, 2R) 1-methyl hydrogen cyclopentane-dicarboxylate, 24 g, and 30 mL of oxalyl chloride in 1.3 L of toluene was stirred for 28 h under a stream of nitrogen to remove HCl. Concentration of the resulting solution gave 23 g of acid chloride as on oil. A solution of the acid chloride in 750 mL of dry tetrahydrofuran containing 15 mL of redistilled 2,6-lutidine and 3 g of 10% palladium on carbon was shaken under 50 psi of hydrogen for 18 h, filtered and concentrated under reduced pressure at 25°C. The residue was diluted with 300 mL of ethyl acetate and washed with 30 mL of 1N hydrochloric acid, 30 mL of saturated sodium bicarbonate and dried ($MgSO_4$). Removal of solvents under reduced pressure gave 20 g of pure cis-aldehyde, homogeneous by HPLC and TLC (10% EtOAc/ hexanes development): $[\alpha]_D^{25} = +60.7^o$ (c=1.57 MeOH).

Step C: (4aS,7aS) Methyl 1-oxo-hexahydro-1H-pyrindene-3-carboxylate

To a stirred solution of 100 mL of commercial 1M lithium bis(trimethylsilyl)amide in THF diluted in 200 mL of THF cooled to -40°C was added a solution of 18 g of the benzylidene derivative of glycine methyl ester [G. Stork, A. Y. W. Leong and A. M. Touzin, J. Amer. Chem. Soc., *41*, 3491-3, 1976] as a solution in 70 mL of THF maintaining the temperature between -40 and -35°C. After 30 min, a solution of 16 g of (1S, 2R) methyl 2-formylcyclopentanecarboxylate in 35 mL of THF was added over 15 min. After 45 min at -40°C, the

reaction was quenched with 30 mL of AcOH and 60 mL of MeOH. After concentration to near dryness, the residue was dissolved in 25 mL of AcOH and 175 mL of MeOH. The resulting mixture was aged for 7 days at 25°C, then concentrated to dryness. Column chromatodgraphy using a gradient of 20%-30% EtOAc/hexanes gave 12 g of the (4aS,7aS) methyl 1-oxo-hexahydro-1H-pyrindene-3-carboxylate. The earlier fractions contained 5 g of lactones which were converted into 2.6 g of additional product by retreatment with 20 mL of AcOH and 100 mL of MeOH.

Step D: (3S,4aS,7aS) Methyl 1-oxo-octahydro-1H-pyrindene-3-carboxylate

Hydrogenation of 12 g of (4aS,7aS) methyl 1-oxo-hexahydro-1H-pyrindene-3-carboxylate in 120 mL of dry THF with 1.1 g of 5% Pd/C under 50 psi of hydrogen on a shaker gave 12 g of product as a crystalline solid: mp 55-58°C; $[\alpha]_D^{25} = +1^o$ (c=1 MeOH); Elemental analysis, calc'd. for $C_{10}H_{15}NO_3$ (197.24):

	C, 60.90;	H, 7.67;	N, 7.10
Found:	C, 61.29;	H, 7.65;	N, 7.07.

Step E: (3S,4aS,7aS) Methyl octahydro-1H-pyrindene-3-carboxylate

A solution of 3 g of (3S,4aS,7aS) methyl 1-oxo-octahydro-1H-pyrindene-3-carboxylate in 50 mL of dry THF was cooled to 0°C and treated dropwise with 3.2 mL of borane methylsulfide complex, maintaining the temperature at 0-5°C. After stirring 3 h at 25°C, the the mixture was cooled and quenched by dropwise addition of 85 mL of 2N HCl maintaining the temperature between 0-5°C. The mixture was allowed to warm to 15°C and stand for 12 h in the refridgerator. The pH adjusted to 10 with 5N NaOH and the mixture extracted 2 X 300 mL of ethyl acetate. The combined extracts gave after drying ($MgSO_4$) and concentration under reduced pressure, 1.9 g of amino ester product as an oil.

Step F: (3S,4aS,7aS) N-tert-Butyl octahydro-1H-pyrindene-3-carboxamide

A solution of 12 mL of trimethylaluminum (2.0M in toluene) and 2.6 mL of tert-butylamine in 10 mL of THF was warmed to 40-45°C for 30 min, cooled to room temperature, concentrated to dryness under reduced pressure and redissolved in 10 mL of dry THF. A solution of 1.2 g of (3S,4aS,7aS) methyl octahydro-1H-pyrindene-3-carboxylate in 5 mL of THF was added and the mixture aged at 25°C for 24 h. The resulting mixture was added to 100 mL of ice cold saturated sodium potassium tartrate and 100 mL of ethyl acetate. After stirring vigorously for 1 h, the organic layer was separated, dried ($MgSO_4$) and concentrated to dryness. There was obtained 1.2 g of crude tert-butyl amide which was essentially homogeneous by TLC.

Step G: (3S,4aS,7aS,2'R,3'S) N-tert-Butyl 2(2'-hydroxy-4'-phenyl-3'-azidobutyl)-octahydro-1H-pyrindene-3-carboxamide

A mixture of 3 g of (3S,4aS,7aS) N-tert-Butyl octahydro-1H-pyrindene-3-carboxamide and 4 g of 3(S)-azido-(1, 2R)-epoxy-4-phenylbutane in 50 mL of isopropanol was heated to 80°C overnight then concentrated to dryness under reduced pressure. Recrystallization from ethyl acetate-hexanes gave 2.16 g of product: mp 91-93°C; Elemental analysis, calc'd. for $C_{23}H_{35}N_5O_2$(413.57):

	C, 66.80;	H, 8.53;	N, 16.93
Found:	C, 66.87;	H, 8.46;	N, 16.54.

Step H: Preparation of (3S,4aS,7aS,2'R,3'S,3"S,3"aR,7"aS) N-tert-Butyl octahydro-2(2'-hydroxy-4'-phenyl-3'(3"-hexahydro-4"H-furo[2,3-b]pyranyloxycarbonylamino)-butyl)-1H-pyrindene-3-carboxamide (Compound E) (L-743,639)

A mixture of 0.050 g of (3S,4aS,7aS,2'R,3'S) N-tert-butyl 2(2'-hydroxy-4'-phenyl-3'-azidobutyl)-octahydro-1H-pyrindene-3-carboxamide, 0.040 g of (3S, 3aR, 7aS) 3-hydroxy-4H-hexahydro-furo[2,3-b]pyranyl 2-pyridyl carbonate, 0.030 g of 10% Pd/C, and

0.041 mL of Et_3N in 5 mL of THF was stirred under an atmosphere of hydrogen for 48 h. Removal of the catalyst by filtration, concentration under reduced pressure and purification by preparative TLC, eluting with ethyl acetate gave 0.050 g of product as a white solid: mp 79-82°C; Elemental analysis, calc'd. for $C_{31}H_{47}N_3O_6$ x 0.15 $CHCl_3$(575.645):

	C, 64.99;	H, 8.26;	N, 7.30
Found:	C, 65.26;	H, 8.16;	N, 7.11.

EXAMPLE 22

(3S,4aS,7aS,2'R,3'S,3"R,3"aS,6"aR) N-tert-Butyl octahydro-2(2'-hydroxy-4'-phenyl-3'(3"-hexahydrofuro[2,3-b]furanyloxycarbonyl-amino)butyl)-1H-pyrindene-3-carboxamide (L-741,129)

From (3R, 3aS, 6aR) 3-hydroxy-4H-hexahydrofuro[2,3-b]furan using the procedure substantially as described above for preparation of Compound E there was obtained a white solid: m.p. °C; Elemental analysis, calc'd. for $C_{30}H_{45}N_3O_6$ (543.71):

	C, 66.27;	H, 8.34;	N, 7.35
Found:	C, 66.32;	H, 8.12;	N, 7.68.

EXAMPLE 23

(3aS,4S,6aR) 4-Hydroxyhexahydro-2H-cyclopenta[b]furan

To a stirred solution of 1.1 g commercial *cis*-(-)-3,3a,6,6a-tetrahydro-2H-cyclopenta[b]furan-2-one in 10 mL anhydrous THF was added 13.3 mL of 2M lithium borohydride in THF to a solution of at room temperature. After stirring overnight the reaction mixture was quenched by the addition of 25 mL of 1N HCl and extracted with ethyl acetate (30 mL x 3). Combined organic layers were dried over $MgSO_4$ and concentrated. Purification of the residue by chromatography gave 420.6 mg of diol. To a stirred solution of 1.3 g of diol in 10 mL of acetonitrile was added 1.3 g of iodine in 10 mL of acetonitrile. After 2 hours saturated Na_2SO_3 was added until the iodine color disappeared

and the mixture was extracted with ethyl acetate (25 mL x 3). Combined organic layers were dried over $MgSO_4$ and concentrated. Purification of the residue by chromatography gave 230 mg of (3aS,4S,6aR) 4-hydroxy-6-iodo-hexahydro-2H-cyclopenta[b]furan. A solution of 230 mg of (3aS,4S,6aR) 4-hydroxy-6-iodo-hexahydro-2H-cyclopenta[b]-furan, 0.37 mL of tri n-butyltinhydride and 10 mg of AIBN in 10 mL of benzene was refluxed overnight. After removal of solvents under reduced pressure, chromatography gave 75 mg of (3aS,4S, 6aR) 4-hydroxyhexahydro-2H-cyclopenta[b]furan.

EXAMPLE 24

(3aR,4R,6aS) 4-Hydroxyhexahydro-2H-cyclopenta[b]furan

From commercial *cis*-(+)-3,3a,6,6a-tetrahydro-2H-cyclopenta[b]furan-2-one using the procedure substantially as described above for preparation of (3aS,4S, 6aR) 4-hydroxyhexahydro-2H-cyclopenta[b]furan there was obtained a clear colorless oil.

EXAMPLE 25

(3S,4aS,8aS,2'R,3'S,3"aS,4"S,6"aR) N-tert-Butyl 2(2'-hydroxy-4'-phenyl-3'-(4"-hexahydro-2H-cyclopenta[b]furanyloxycarbonylamino)-butyl)-decahydroisoquinoline-3-carboxamide(L-743,707)

From (3aS,4S, 6aR)-4-hydroxyhexahydro-2H-cyclopenta[b]furan using the procedure substantially as described above for preparation of Compound C there was obtained a white solid: m.p. 87-8°C; Elemental analysis, calc'd. for $C_{32}H_{48}N_3O_5 \times 0.5\ CH_3CO_2CH_2CH_3$ (598.81):

	C, 68.20;	H, 8.75;	N, 7.02
Found:	C, 68.27;	H, 8.71;	N, 6.96.

EXAMPLE 26

(3S,4aS,8aS,2'R,3'S,3"aR,4"R,6"aS) N-tert-Butyl 2(2'-hydroxy-4'-phenyl-3'-(4"-hexahydro-2H-cyclopenta[b]furanyloxycarbonylamino)-butyl)-decahydroisoquinoline-3-carboxamide (L-743,770)

From (3aR,4R, 6aS)-4-hydroxyhexahydro-2H-cyclopenta[b]furan using the procedure substantially as described above for preparation of Compound C there was obtained a white solid: m.p. 85-7°C; Elemental analysis, calc'd. for $C_{32}H_{48}N_3O_5$ x 0.35 $CHCl_3$ (597.54):

	C, 65.03;	H, 8.32;	N, 7.03
Found:	C, 65.04;	H, 8.36;	N, 6.83.

EXAMPLE

Assay for Inhibition of Microbial Expressed HIV Protease

Inhibition studies of the reaction of the HIV protease expressed in Escherichia coli with a peptide substrate [Val-Ser-Gln-Asn-(betanapthyl)Ala-Pro-Ile-Val, 0.5 mg/mL at the time the reaction is initiated] were in 50 mM Na acetate, pH 5.5, at 30°C for 1 hour. Various concentrations of inhibitor in 1.0 ul DMSO were added to 25 ul of the peptide solution in water. The reaction is initiated by the addition of 15 ul of 0.33 nM protease (0.11 ng) in a solution of 0.133 M Na acetate pH 5.5 and 0.26% bovine serum albumin. The reaction was quenched with 160 ul of 5% phosphoric acid. Products of the reaction were separated by HPLC (VYDAC wide pore 5 cm C-18 reverse phase, acetonitrile gradient, 0.1% phosphoric acid). The extent of inhibition of the reaction was determined from the peak heights of the products. HPLC of the products, independently synthesized, proved quantitation standards and confirmation of the product composition. Compounds B and C showed IC_{50} values of about 1.0 nM, and 1.5 nM respectively.

CELL SPREAD ASSAY

Inhibition of the spread of HIV in cell culture was measured according to Nunberg, J. H. et al., J. Virol. 65, 4887 (1991). In this assay, MT-4 T-lymphoid cells were infected with HIV-1 by using a predetermined inoculum, and cultures were incubated for 24h. At this time, ≤1% of the cells were positive by indirect immunofluorescence. Cells were then extensively washed and distributed into 96-well culture dishes. Serial twofold dilutions of inhibitor were added to the wells, and cultures were continued for 3 additional days. At 4 days postinfection, 100% of the cells in control cultures were infected. HIV-1 p24 accumulation was directly correlated with virus spread. The cell culture inhibitory concentration was defined as the inhibitor concentration which reduced the spread of infection by at least 95%, or CIC95. Because all virus populations appeared monodisperse and displayed parallel dose-response curves, resistance was quantified as the ratio of inhibitor concentrations that reduced the spread of infection by at least 95%. Compounds B and C each showed CIC95 values of about 25-50 nM.

INHIBITION OF VIRUS SPREAD

A. Preparation of HIV-infected MT-4 cell Suspension

MT cells are infected at Day 0 at a concentration of 250,000 per ml with a 1:1000 dilution of HIV-1 strain IIIb stock (final 125 pg p24/ml; sufficient to yield ≤1% infected cells on day 1 and 25-100% on day 4). Cells are infected and grown in the following medium: RPMI 1640 (Whittaker BioProducts), 10% inactivated fetal bovine serum, 4 mM glutamine (Gibco Labs) and 1:100 Penicillin-Streptomycin (Gibco Labs).

The mixture is incubated overnight at 37°C in 5% CO_2 atmosphere.

B. Treatment with Inhibitors

A matrix of nanomolar range concentrations of the pairwise combinations (see Table S) is prepared. At Day 1, aliquots of 125 µl of inhibitors are added to equal volumes of HIV-infected MT-4 cells (50,000 per well) in a 96-well microtiter cell culture plate. Incubation is continued for 3 days at 37°C in 5% CO_2 atmosphere.

C. Measurement of Virus Spread

Using a multichannel pipettor, the settled cells are resuspended and 125 µl harvested into a separate microtiter plate. The supernatant is assayed for HIV p24 antigen.

The concentration of HIV p24 antigen is measured by an enzyme immunoassay, described as follows. Aliquots of p24 antigen to be measured are added to microwells coated with a monoclonal antibody specific for HIV core antigen. The microwells are washed at this point, and at other appropriate steps that follow. Biotinylated HIV-specific antibody are then added, followed by conjugated strepavidin-horseradish peroxidase. A color reaction occurs from the added hydrogen peroxide and tetramethylbenzidine substrate. Color intensity is proportional to the concentration of HIV p24 antigen.

Calculation of Degree of Synergy

Pairwise combinations of inhibitors (see Table 5) are found to exhibit markedly enhanced inhibition of virus spread, in comparison to each inhibitor alone, or in comparison to merely additive inhibition of each inhibitor.

This data is processed as follows: fractional inhibitory concentration ratios (FIC) are calculated according to Elion, et. al. J. Biol. Chem., 208, 477 (1954). The minimum sum of FICS, which is the maximum synergy, is determined for various pairwise combinations. Alternatively, the average sum of FICS can be calculated. See Table S. These results indicate substantial synergy in the inhibition of virus spread. The smaller the number, the greater the synergy.

TABLE S

Pairwise Combinations*			Maximum Synergy
684	+	ddI	
684	+	AZT	
684	+	661	

* 684 is L-739,684, which is Compound B.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations, or modifications, as come within the scope of the following claims and its equivalents.

WHAT IS CLAIMED IS:

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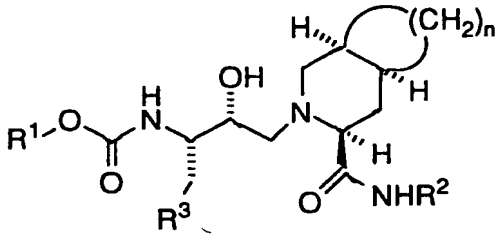


(I)

wherein:

n is 3 or 4;

R^1 is a 7- to 10-membered bicyclic heterocycle, either ring of which is saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S, wherein the nitrogen or sulfur heteroatoms may optionally be oxidized, said heterocycle being unsubstituted or substituted with one or more of C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-3} alkoxy, halo-C_{1-3} alkyl, aryl-C_{1-3} alkyl, C_{3-5} cycloalkyl, di-C_{1-3}-alkyl-amino-C_{1-4}-alkyl, halo or aryl;

R^2 is

a) C_{1-5} alkyl, unsubstituted or substituted with one or more of -OH or C_{1-3} alkoxy; or

b) 5- to 7-membered carbocyclic ring which is either saturated, partially saturated or unsaturated, the carbocyclic ring being unsubstituted or substituted with one or more of C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-3} alkoxy, or hydroxy;

R^3 is

a) Phenyl unsubstituted or substituted with one or more of -OH or C_{1-3} alkoxy; or

b) C_{5-7} cycloalkyl unsubstituted or substituted with one or more of -OH or C_{1-3} alkoxy,

or pharmaceutically acceptable salt or hydrate thereof.

2. A compound according to Claim 1,

wherein:

R^1 is a 7- to 10-membered bicyclic heterocycle, either ring of which is saturated or unsaturated, and which consists of carbon atoms and from one to three oxygen heteroatoms, said heterocycle being unsubstituted or substituted with one or more of C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-3} alkoxy, halo-C_{1-3} alkyl, aryl-C_{1-3} alkyl, C_{3-5} cycloalkyl, di-C_{1-3} alkyl-amino- C_{1-4} alkyl, halo or aryl;

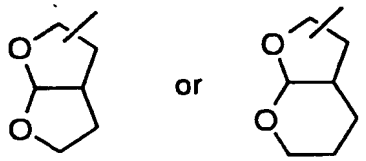
R^2 is C_{1-5} alkyl, unsubstituted or substituted with one or more of -OH;

R^3 is phenyl unsubstituted or substituted with -OH or C_{1-3} alkoxy.

3. A compound according to Claim 2

wherein:

R^1 is a bicyclic heterocycle of the structures:



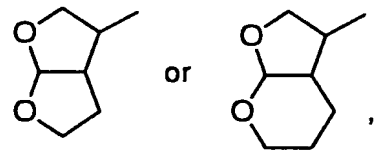
said heterocycle unsubstituted or substituted once with C_{1-4} alkyl, methoxy, dimethylaminomethyl, halo or aryl;

R^2 is t-butyl or 2-methylpropyl;

R^3 is phenyl.

4. A compound according to Claim 3, wherein

R^1 is



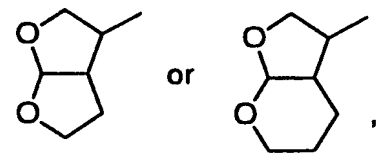
either of which is unsubstituted or substituted once with C_{1-4} alkyl, methoxy, dimethylaminomethyl, halo or aryl;

R^2 is t-butyl or 2-methylpropyl;

R^3 is phenyl.

5. A compound according to Claim 4, wherein

R^1 is



and,

R^2 is t-butyl;

R^3 is phenyl.

6. A compound, which is

(3S,4aS,8aS,2'R,3'S,3"S,3"aR,5"R,7"aS) N-tert-butyl 2(2'-hydroxy-4'-phenyl-3'(6"-methyl-3"-hexahydro-4H-furo[2,3-b]pyranyloxy-carbonylamino)butyl)-decahydroisoquinoline-3-carboxamide,

(3S,4aS,8aS,2'R,3'S,3"R,3"aS,5"S,6"aR) N-tert-butyl 2(2'-hydroxy-4'-phenyl-3'(5"-methyl-3"-hexahydrofuro[2,3-b]furanyloxy-carbonylamino)butyl)-decahydroisoquinoline-3-carboxamide (L-739,783),

(3S,4aS,8aS,2'R,3'S,2"S,3"S,3"aR,7"aS) and (3S,4aS,8aS,2'R,3'S,2"R,3"R,3"aS,7"aR) N-tert-Butyl 2(2'-hydroxy-4'-phenyl-3'(2"-methyl-3"-hexahydro-4"H-furo[2,3-b]pyranyloxy-carbonylamino)butyl)-decahydroisoquinoline-3-carboxamide (L-743,787),

(3S,4aS,8aS,2'R,3'S,2"R,3"S,3"aR,7"aS) and (3S,4aS,8aS,2'R,3'S,2"S,3"R,3"aS,7"aR) N-tert-Butyl 2(2'-hydroxy-4'-phenyl-3'(2"-methyl-3"-hexahydro-4"H-furo[2,3-b]pyranyloxy-carbonylamino)butyl)-decahydroisoquinoline-3-carboxamide (L-743,788),

(3S,4aS,8aS,2'R,3'S,2"S,3"S,3"aR,6"aS) and (3S,4aS,8aS,2'R,3'S,2"R,3"R,3"aS,6"aR) N-tert-Butyl 2(2'-hydroxy-4'-phenyl-3'(2"-methyl-3"-hexahydrofuro[2,3-b]furanyloxycarbonyl-amino)butyl)-decahydroisoquinoline-3-carboxamide,

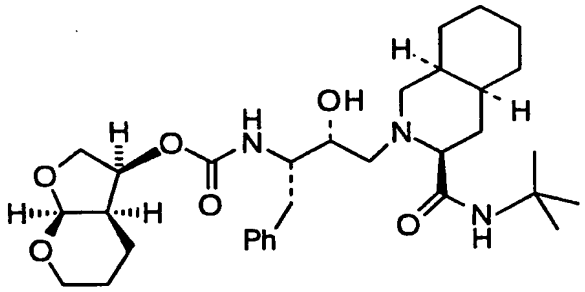
(3S,4aS,8aS,2'R,3'S,3"R,3"aS,5"R,6"aR) N-tert-butyl 2(2'-hydroxy-4'-phenyl-3'(5"-methyl-3"-hexahydrofuro[2,3-b]furanyloxy-carbonylamino)butyl)-decahydroisoquinoline-3-carboxamide L-743,768),

(3S,4aS,8aS,2'R,3'S,3"aS,4"S,6"aR) N-tert-Butyl 2(2'-hydroxy-4'-phenyl-3'-(4"-hexahydro-2H-cyclopenta[b]furanyloxycarbonylamino)-butyl)-decahydroisoquinoline-3-carboxamide (L-743,707), or

(3S,4aS,8aS,2'R,3'S,3"aR,4"R,6"aS) N-tert-Butyl 2(2'-hydroxy-4'-phenyl-3'-(4"-hexahydro-2H-cyclopenta[b]furanyloxycarbonylamino)-butyl)-decahydroisoquinoline-3-carboxamide (L-743,770),

or pharmaceutically acceptable salts thereof.

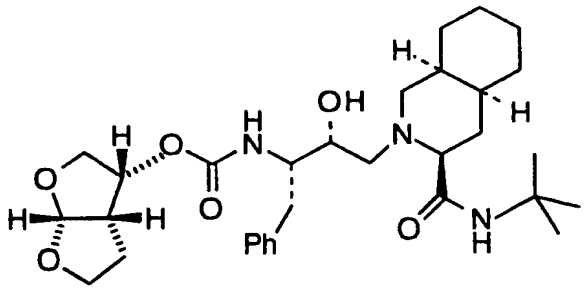
7. The compound



named:
(3S,4aS,8aS,2'R,3'S,3"S,3"aR,7"aS) N-tert-Butyl 2(2'-hydroxy-4'-phenyl-3'(3"-hexahydro-4"H-furo[2,3-b]pyranyloxycarbonyl-amino)butyl)-decahydroisoquinoline-3-carboxamide,
or pharmacuetically acceptable salt thereof.

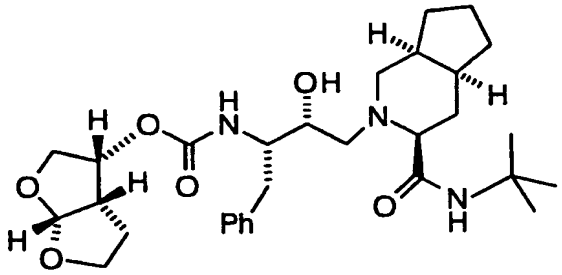
8. The compound

C:



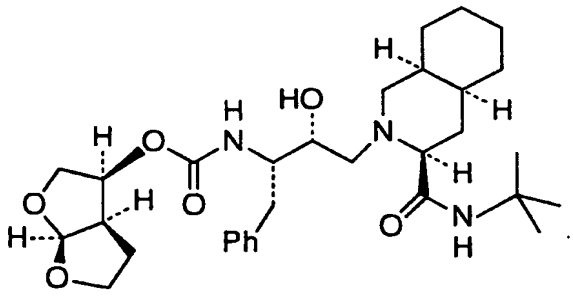
named:
(3S,4aS,8aS,2'R,3'S,3"R,3"aS,6"aR) N-tert-butyl 2(2'-hydroxy-4'-phenyl-3'(3"-hexahydrofuro[2,3-b]furanyloxycarbonylamino)butyl)-decahydroisoquinoline-3-carboxamide,
or pharmaceutically acceptable salt thereof.

9. The compound [L-741,129]



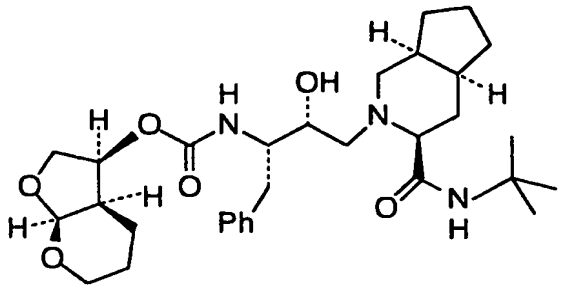
named:
(3S,4aS,7aS,7aS,2'R,3'S,3"R,3"aS,6"aR) N-tert-Butyl octahydro-2(2'-hydroxy-4'-phenyl-3'(3"-hexahydrofuro[2,3-b]furanyloxycarbonyl-amino)butyl)-1H-pyrindene-3-carboxamide,
or pharmaceutically acceptable salt thereof.

10. The compound, [L-739,663]



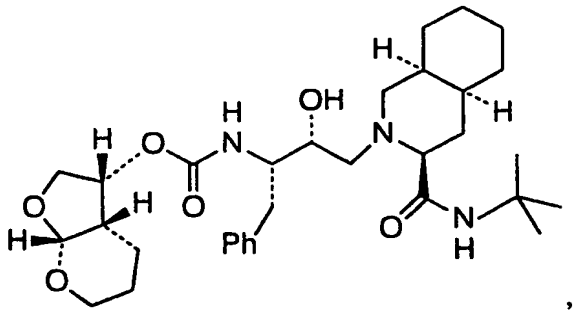
named:
(3S,4aS,8aS,2'R,3'S,3"S,3"aR,6"aS) N-tert-butyl 2(2'-hydroxy-4'-phenyl-3'(3"-hexahydrofuro[2,3-b]furanyloxycarbonylamino)butyl)-decahydroisoquinoline-3-carboxamide,
or pharmaceutically acceptable salt thereof.

11. The compound, [L-743,639]



named:
(3S,4aS,7aS,2'R,3'S,3"S,3"aR,7"aS) N-tert-butyl octahydro-2(2'-hydroxy-4'-phenyl-3'(3"-hexahydrofuro-4"H-furo[2,3-b]pyranyloxy-carbonylamino)butyl)-1H-pyrindene-3-carboxamide,
or pharmaceutically acceptable salt thereof.

12. The compound, [L-739,761]



named:
(3S,4aS,8aS,2'R,3'S,3"R,3"aS,7"aR) N-tert-butyl 2(2'-hydroxy-4'-phenyl-3'(3"-hexahydrofuro-4"H-furo[2,3-b]pyranyloxycarbonyl-amino)butyl)-decahydroisoquinoline-3-carboxamide,
or pharmaceutically acceptable salt thereof.

13. Pharmaceutical composition, for use in the treatment of AIDS, in the prevention of infection by HIV, in the treatment of infection of HIV, or in the inhibition of HIV protease, comprising an effective amount of a compound as in any of Claims 1-12, and a pharmaceutically acceptable carrier.

14. A method of treating AIDS, comprising administering an effective amount of a compound as in any Claims 1-12.

15. A method of preventing infection by HIV, comprising administering an effective amount of a compound as in any of Claims 1-12.

16. A method of treating infection by HIV, comprising administering an effective amount of a compound as in any of Claims 1-12.

17. A method of inhibiting HIV protease, comprising administering an effective amount of a compound as in any of Claims 1-12.

18. A synergistic combination of compounds, which is either L-739,684 or L-739,594, and L-697,661, and, optionally, AZT or ddI or ddC.

19. A synergistic combination of compounds, which is either L-739,684 or L-739,594, and any of AZT or ddI or ddC.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 94/05128

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D493/04 C07D405/12 A61K31/47 A61K31/35 A61K31/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y X	EP,A,0 539 192 (MERCK & CO. INC.) 28 April 1993 *see compound on page 17, second from bottom* ---	1-13,18, 19 1-3,13
A	EP,A,0 346 847 (F HOFFMANN-LA ROCHE AG) 20 December 1989 *see whole document and also compounds of formula IX on page 11* ---	1-13,18, 19
A	J. MED. CHEM. vol. 35 , 1992 pages 2525 - 2533 T.J.TUCKER ET AL 'A series of potent HIV-1 protease inhibitors containing a hydroxyethyl secondary amine transition state isostere' *see especially compounds 7a and 7b* --- -/--	1-13,18, 19

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
12 August 1994	26. 08. 94

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European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Scruton-Evans, I

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INTERNATIONAL SEARCH REPORT

Inte. ional Application No
PCT/US 94/05128

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	EP,A,0 434 365 (MERCK & CO. INC.) 26 June 1991 *see whole document, and especially pages 28/29* -----	1-13,18, 19

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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